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| (21) International Application Number: PCT/SE96/01635 (22) International Filing Date: 11 December 1996 (11.12.96) (30) Priority Data: 9504661-1 22 December 1995 (22.12.95) SE (71) Applicant (for all designated States except MG US): ASTRA PHARMA INC. [CA/CA]; 1004 Middlegate Road, Mississauga, Ontario L4Y 1M4 (CA). (71) Applicant (for MG only): ASTRA AKTIEBOLAG (publ) [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): ROBERTS, Edward [GB/CA]; 2541 Chestnut Circle, St. Lazare de Vaudreuil, Quebec J7T 2A1 (CA). PLOBECK, Niklas [SE/CA]; Apartment 412, 4655 Boulevard Henri-Bourassa West, Ville St. Laurent, Quebec H4L 5H6 (CA). WAHLESTEDT, Claes [SE/CA]; 6 Chelsea Place, Montreal, Quebec H3G 2J9 (CA). (74) Agent: ASTRA AKTIEBOLAG; Patent Dept., S-151 85 Södertälje (SE). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. |
| (54) Title: NOVEL COMPOUNDS WITH ANALGESIC EFFECT (57) Abstract Compounds of formula (I) as well as their pharmaceutically acceptable salts, and pharmaceutical compositions comprising the novel compounds. The novel compounds of formula (I) are useful in the management of pain. <div data-bbox="1088 1134 1347 1386"><chem>*N1CC(R3)C(R3)C(R2)(A)C(R4)C1R6</chem></div> | | |

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NOVEL COMPOUNDS WITH ANALGESIC EFFECT

Field of the invention

- 5 The present invention is related to novel compounds, to a process for their preparation, their use and pharmaceutical compositions comprising the novel compounds. The novel compounds are used in therapy, and in particular for the treatment of pain.

10 Background and prior art

The δ receptor has been identified as having a role in many bodily functions such as circulatory and pain systems. Ligands for the δ receptor may therefore find potential use as analgesics, and/or as antihypertensive agents. Ligands for the δ receptor have also been
15 shown to possess immunomodulatory activities.

The identification of at least three different populations of opioid receptors (μ , δ and κ) is now well established and all three are apparent in both central and peripheral nervous systems of many species including man. Analgesia has been observed in various animal
20 models when one or more of these receptors has been activated.

With few exceptions, currently available selective opioid δ ligands are peptidic in nature and are unsuitable for administration by systemic routes. Some non-peptidic δ antagonists have been available for some time (see Takemori and Portoghese, 1992, Ann. Rev. Pharmacol.
25 Tox., 32: 239-269. for review). These compounds, *e.g.* naltrindole, suffer from rather poor (*i.e.*, < 10-fold) selectivity for the δ receptor vs μ ' receptor binding and exhibit no analgesic activity, a fact which underscores the need for the development of highly selective non-peptidic δ agonists..

Recently, a non-peptidic δ agonist, BW 373U86, was described by Chang *et al.*, 1993, J. Pharmacol. Exp. Ther., 267: 852-857., as the first δ -selective non-peptide with analgesic activity, however, it shows significant affinity for the μ receptor.

- 5 Thus, the problem underlying the present invention was to find new analgesics having excellent analgesic effects, but also with an improved side-effect profile over current μ agonists and potential oral efficacy.

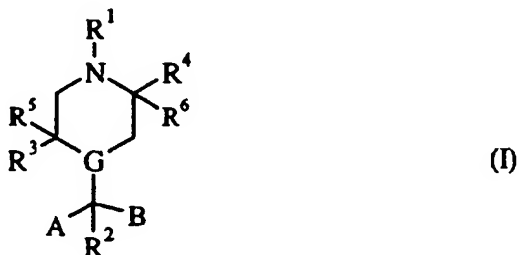
- Analgesics that have been identified and are existing in the prior art have many
10 disadvantages in that they suffer from poor pharmacokinetics and are not analgesic when administered by systemic routes. Also, it has been documented that preferred compounds, described within the prior art, show significant convulsive effects when administered systemically.

- 15 In WO 93/15062 and WO 95/045051, some diarylmethylpiperazine and diarylmethylpiperidine compounds, including BW 373U86, are disclosed, but these prior art compounds are structurally distinct from the compounds according to the present invention.

- The problem mentioned above has been solved by developing novel piperazine and
20 piperidine compounds, as will be described below.

Outline of the invention

The novel compounds according to the present invention are defined by the formula (I)



5

wherein

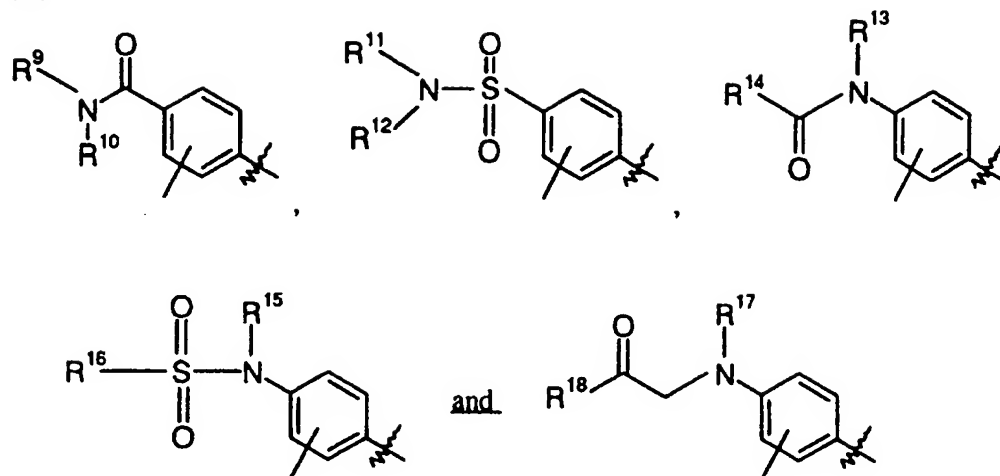
G is a carbon atom or a nitrogen atom;

10 A is selected from

(i) phenyl substituted by any of -COOH, -CONH₂, COOCH₃, -CN, NH₂ or -COCH₃;

15 (ii) naphthyl, benzofuranyl, and quinoliny; and

(iii)



wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3 , $(\text{CH}_2)_o\text{CF}_3$, halogen, CONR^7R^8 , CO_2R^7 , COR^7 , $(\text{CH}_2)_o\text{NR}^7\text{R}^8$, $(\text{CH}_2)_o\text{CH}_3(\text{CH}_2)_o\text{SOR}^7$, $(\text{CH}_2)_o\text{SO}_2\text{R}^7$ and $(\text{CH}_2)_o\text{SO}_2\text{NR}^7\text{R}^8$ wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1 is selected from hydrogen; a branched or straight C_1 - C_6 alkyl, C_1 - C_6 alkenyl, $-\text{CO}(\text{C}_1$ - C_6 alkyl); $(\text{C}_1$ - C_6 alkyl)-B wherein B is as defined below; C_3 - C_8 cycloalkyl, C_4 - C_8 (alkyl-cycloalkyl) wherein alkyl is C_1 - C_2 alkyl and cycloalkyl is C_3 - C_6 cycloalkyl; C_6 - C_{10} aryl; and heteroaryl having from 5 - 10 atoms selected from any of C, S, N and O; and whereby the C_6 - C_{10} aryl and the heteroaryl may optionally be substituted by 1 or 2 substituents selected from hydrogen, CH_3 , $(\text{CH}_2)_o\text{CF}_3$, halogen, CONR^7R^8 , CO_2R^7 , COR^7 , $(\text{CH}_2)_o\text{NR}^7\text{R}^8$, $(\text{CH}_2)_o\text{CH}_3(\text{CH}_2)_o\text{SOR}^7$, $(\text{CH}_2)_o\text{SO}_2\text{R}^7$ and $(\text{CH}_2)_o\text{SO}_2\text{NR}^7\text{R}^8$, wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^7 and R^8 is each and independently as defined for R^1 above;

R^2 is selected from hydrogen, CH_3 , OR^1 , CO_2R^1 , and $\text{CH}_2\text{CO}_2\text{R}^1$ wherein R^1 is as defined above;

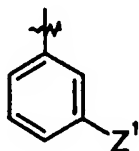
$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}$, and R^{18} , is each and independently as defined for R^1 above;

- 5 B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety, each having from 5 to 10 atoms selected from any of C, S, N and O, and each being optionally and independently substituted by 1 or 2 substituents independently selected from hydrogen, CH_3 , CF_3 , halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7 ,
 10 $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$, and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, 2 or 3 and wherein R^7 and R^8 are as defined above;

- R^3, R^4, R^5 and R^6 is each and independently selected from
 15 R^7 , $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p(p-OH Ph)$, $(CH_2)_p-3-indolyl$, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$;
 wherein p is 0, 1, 2, 3, or 4, and R^7 and R^8 are as defined above;

- with the proviso that when A is a phenyl ring substituted by a -CN group or by a
 20 $-NH_2$ group, B may not be



wherein

- Z^1 is hydroxy, and esters thereof;
 25 hydroxymethyl, and esters thereof; or
 amino, and carboxamides and sulfonamides.

Within the scope of the invention are also pharmaceutically acceptable salts of the compounds of the formula (I), as well as isomers, hydrates, isoforms and prodrugs thereof.

Preferred compounds according to the invention are compounds of the formula (I)

5 wherein

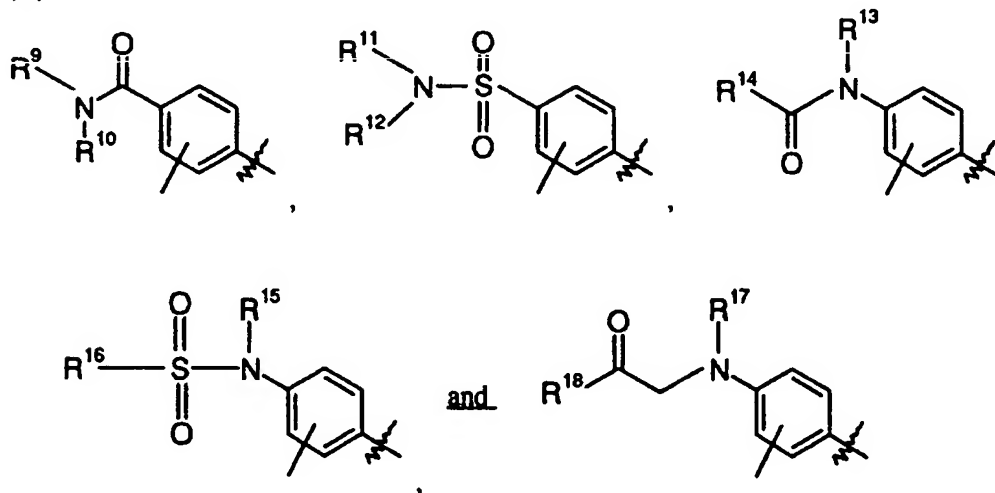
G is a carbon atom or a nitrogen atom;

A is selected from

10 (i) phenyl substituted by any of -COOH, -CONH₂, COOCH₃, -CN, NH₂ or -COCH₃;

(ii) naphthyl, benzofuranyl, and quinoliny; and

15 (iii)



20

wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH₃, (CH₂)_oCF₃, halogen, CONR⁷R⁸, CO₂R⁷, COR⁷, (CH₂)_oNR⁷R⁸, (CH₂)_oCH₃(CH₂)_oSOR⁷, (CH₂)_oSO₂R⁷ and (CH₂)_oSO₂NR⁷R⁸, wherein o is 0, 1, or 2, and R⁷ and R⁸ are as defined below;

25

R^1 , R^7 and R^8 is each and independently selected from hydrogen; a branched or straight C_1 - C_4 alkyl, allyl, $-\text{CO}-(C_1-C_6 \text{ alkyl})$; $(C_1-C_6 \text{ alkyl})-B$ wherein B is as defined below; C_3 - C_5 cycloalkyl, C_4 - C_8 (alkyl-cycloalkyl) wherein alkyl is C_1 - C_2 alkyl and cycloalkyl is C_3 - C_6 cycloalkyl; and phenyl;

5

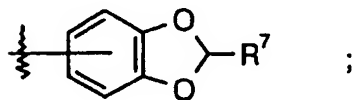
R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , and R^{18} , is each and independently as defined for R^1 above;

10

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrrolyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolyl, and

15



each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3 , CF_3 , halogen, $(\text{CH}_2)_p\text{CONR}^7\text{R}^8$, $(\text{CH}_2)_p\text{NR}^7\text{R}^8$, $(\text{CH}_2)_p\text{COR}^7$,

20

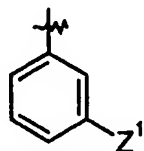
$(\text{CH}_2)_p\text{CO}_2\text{R}^7$, and OR^7 ;

wherein p is 0 or 1, and wherein R^7 and R^8 are as defined above; and

R^3 , R^4 , R^5 and R^6 is each and independently selected from hydrogen, CH_3 , $\text{CH}(\text{Me})_2$, $\text{CH}_2\text{CH}(\text{Me})_2$, $\text{CH}(\text{Me})\text{CH}_2\text{CH}_3$, $(\text{CH}_2)_p\text{CONR}^7\text{R}^8$, $(\text{CH}_2)_p\text{NR}^7\text{R}^8$, $(\text{CH}_2)_p\text{CONR}^7\text{R}^8$, $(\text{CH}_2)_p\text{CO}_2\text{R}^7$, $(\text{CH}_2)_p\text{Ph}$, $(\text{CH}_2)_p(\text{p-OH Ph})$, $(\text{CH}_2)_p$ -3-indolyl, $(\text{CH}_2)_p\text{SR}^7$, and $(\text{CH}_2)_p\text{OR}^7$, wherein p is 0, 1, 2, or 3, and wherein R^7 and R^8 are as defined above;

25

with the proviso that when A is a phenyl ring substituted by a -CN group or by a -NH₂ group, B may not be



5 wherein

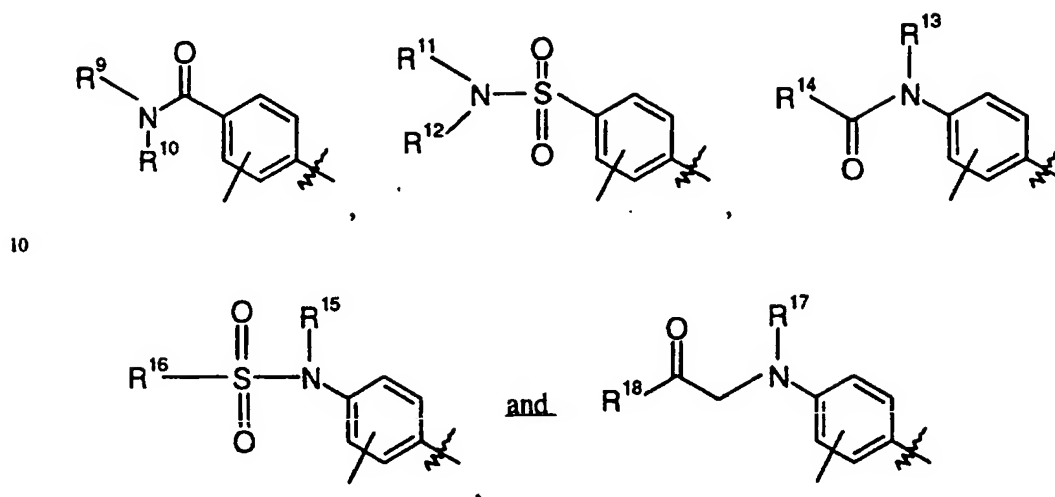
Z¹ is hydroxy, and esters thereof;

hydroxymethyl, and esters thereof; or

amino, and carboxamides and sulfonamides.

Especially preferred compounds according to the invention are compounds of the formula (I) wherein

- 5 G is a nitrogen atom;
A is selected from



wherein

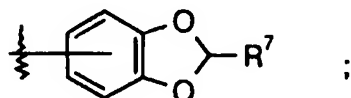
- 15 $R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}$, and R^{18} is each an ethyl group;

R^1 is selected from hydrogen, methyl, ethyl, allyl, or CH_2 -cyclopropyl;

- 20 R^2 is H, methyl, or OR^1 , wherein R^1 is as defined above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinoliny, isoquinoliny, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinoliny, tetrahydrofuranyl, indazoliny, and

5



each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷,
 10 (CH₂)_pCO₂R⁷, and OR⁷,

wherein p is 0, 1, or 2, and wherein R⁷ and R⁸ are as defined for R¹ above;

R³, R⁴, R⁵ and R⁶ is each and independently selected from H, CH₃, CH(Me)₂,
 15 CH₂CH(Me)₂, CH(Me)CH₂CH₃ (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷R⁸,
 (CH₂)_pCO₂R⁷, (CH₂)_pPh, (CH₂)_p(p-OH Ph), (CH₂)_p-3-indolyl, (CH₂)_pSR⁷, and
 (CH₂)_pOR⁷.

wherein p is 0, 1 or 2, and wherein R⁷ and R⁸ are as defined above;

20

The substituents A and B respectively, may optionally be substituted at any position of the ring.

25 By "halogen" we mean chloro, fluoro, bromo and iodo.

By "aryl" we mean an aromatic ring having from 6 - 10 carbon atoms, such as phenyl and naphthyl.

By "heteroaryl" we mean an aromatic ring in which one or more of the 5 -10 atoms in the ring are elements other than carbon, such as N, S and O.

5 By "hydroaromatic" we mean a partly or fully saturated aromatic ring structure having 5-10 carbon atoms in the ring.

By "heterohydroaromatic" we mean a partly or fully saturated aromatic ring structure in which one or more of the 5-10 atoms in the ring are elements other than carbon, such as N,
10 S and O.

By "isomers" we mean compounds of the formula (I), which differ by the position of their functional group and/or orientation. By "orientation" we mean stereoisomers, diastereoisomers, regioisomers and enantiomers.

15

By "isoforms" we mean compounds of the formula (I) which differ by their crystal lattice, such as crystalline compound and amorphous compounds.

By "prodrug" we mean pharmacologically acceptable derivatives, e.g. esters and amides,
20 such the resulting biotransformation product of the derivative is the active drug. The reference by Goodman and Gilmans, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15, describing prodrugs generally, is hereby incorporated.

25 The novel compounds of the present invention are useful in therapy, especially for the treatment of pain.

The compounds are also useful for modulating the analgesic effects acting at the μ opioid receptor subtype, the modulation of side effects seen with agents acting at the μ opioid

receptor subtype such as morphine, especially respiratory depression, gut motility and abuse liability.

Compounds of the invention are also useful as immunomodulators, especially for
5 autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction
10 of opioid receptors is present or implicated in that paradigm. This may involve the use of isotopically labeled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhea, depression, urinary
15 incontinence, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

20 The best mode of performing the present invention known at present, is to use the compounds according to Example 21 (compound 33), Example 22 (compound 34), Example 23 (compound 37), Example 24 (compound 38), Example 25 (compound 41), Example 26 (compound 42), Example 27 (compound 45), Example 29 (compound 51), Example 30 (compound 54), Example 35 (compound 64), Example 36 (compound 65),
25 Example 50, and Example 51. The numbering of the compounds is in accordance with the Examples below, as well as in accordance with the numbering in the Schemes presented in the following.

Methods of preparation

Generalized Method A

5 An aldehyde or ketone is treated with a nucleophile such as a Grignard or organolithium species to produce the corresponding alcohol. This alcohol may then be converted into a suitable leaving group (X) such as an ester, sulphonate or halide which may in turn be displaced with a nucleophilic species such as a substituted or unsubstituted piperazine. N-(4)-unsubstituted piperazine derivatives may then be suitably substituted with a variety of
10 groups via their organo halide or equivalent species, or acylated with a number of different acylating compounds. This sequence of events will give rise to compounds according to general formula I.

Generalized Method B

15 An N-protected amino acid, as its activated ester, may be reacted with a second amino acid ester. On treatment with an acid this species may then cyclize to form a piperazinedione. This dione may be reduced via a number of standard methods to the corresponding piperazine (*e.g.* a reducing agent such as lithium aluminium hydride, by conversion to the
20 thioamide and subsequent desulphurization, hydrogenation in the presence of POCl₃ etc.) This piperazine may then be alkylated or acylated on one or more of the nitrogens and/or may be used subsequently in generalized method A.

Deprotection of functional groups or further modifications may then be necessary, these are
25 described for each individual case. Specific examples for the above transformations are given in the experimental.

All transformations contemplated use reagents (including salts) and solvents known to the art of chemistry and to biotransformations carried out in a suitable biological medium to bring about these transformations and includes all reaction enhancing agents (*e.g.* HMPA), and chiral resolutions using chiral salt formation and chiral biological resolutions.

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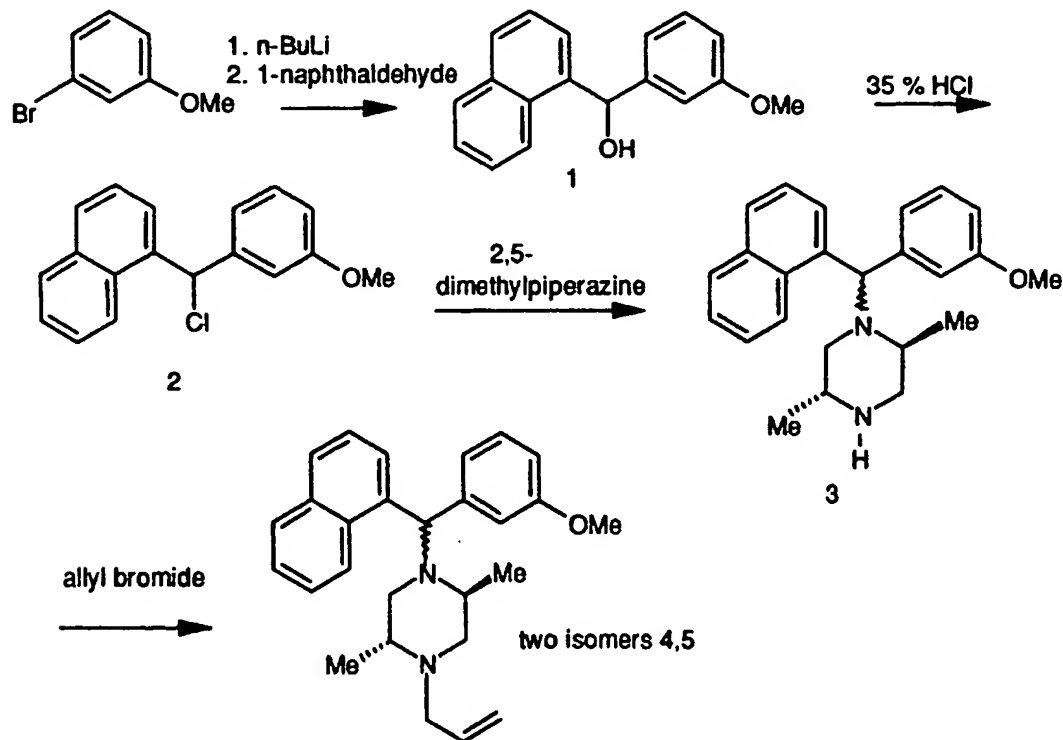
Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not
10 to be construed as limiting the invention.

Scheme 1

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole
(4 & 5).

15



EXAMPLES

The compounds according to Examples 1-3 were synthesized as shown in Scheme 1 above.

5

A.

I. Preparation of 3-methoxy- α -(1-naphthyl)benzyl alcohol (compound 1)

To a solution of 3-bromoanisole (5.61 g, 30.0 mmol) in dry THF (80 mL) was dropwise
10 added n-butyl lithium-hexane solution (1.6 M, 37.5 mL, 60 mmol) under nitrogen at -78°C .
The reaction mixture was allowed to warm to r.t. in 2h and cooled down again to -78°C
prior to addition of 1-naphthaldehyde (4.69 g, 30.0 mmol, in 10 mL THF). The mixture was
warmed to r.t. in 3h, and then quenched with aqueous NH_4Cl solution, extracted with ethyl
acetate (3×50 mL). The combined organic phases were washed with brine, dried over
15 MgSO_4 . Removal of solvents *in vacuo* provided 3-methoxy- α -(1-naphthyl)benzyl alcohol
(4.25 g, 54%). GC-MS ($R_t = 10.41$ min) 264 (M^+), 245, 231, 215, 202, 155, 135, 128,
109.

II. Preparation of 3-methoxy- α -(1-naphthyl)benzyl chloride (compound 2)

20

To a solution of 3-methoxy- α -(1-naphthyl)benzyl alcohol (2.5 g, 9.5 mmol) in diethyl ether
(5 mL) was added 35% hydrochloric acid (10 mL) at 0°C . The reaction mixture was
warmed to r.t. in 1h, and then extracted with ethyl acetate (3×50 mL). The combined
organic layers were washed with aqueous NH_4Cl solution and brine, dried over MgSO_4 .
25 Evaporation of solvents gave 3-methoxy- α -(1-naphthyl)benzyl chloride (1.94 g, 72%). GC-
MS ($R_t = 10.30$ min) 282 (M^+), 247, 232, 215, 202, 189, 163, 151, 139, 123, 101.

Example 1**Preparation of (±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 3)**

- 5 A mixture of *trans*-2,5-dimethylpiperazine (456 mg, 4.0 mmol), 3-methoxy-α-(1-naphthyl)benzyl chloride (430 mg, 1.5 mmol) and triethylamine (2 mL) in dry DMF (10 mL) was refluxed for 2h under nitrogen. after cooling down to r.t., the reaction mixture was quenched with 1 N aqueous NH₄OH solution, and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 0.5 N aqueous NaOH solution, saturated
10 aqueous NH₄Cl and brine, dried over MgSO₄. Removal of solvents gave (±)-trans-1-(3-methoxy-α-(1'-naphthyl)benzyl)-2,5-dimethylpiperazine, which was used directly in the next step: GC-MS (two isomers: R_t = 12.98 & 13.10 min) 360 (M⁺), 301, 276, 247, 232, 215, 189, 165, 131, 113.

15 Example 2 and 3**Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole (compounds 4 & 5)**

- A mixture of above (±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine,
20 K₂CO₃ (276 mg, 2.0 mmol) and allyl bromide (242 mg, 2.0 mmol) in DMF (5 mL)/THF (10 mL) was stirred for 3h at r.t. The reaction mixture was quenched with 1 N NH₄OH and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with saturated aqueous NH₄Cl and brine, dried over MgSO₄. Evaporation of solvents provided crude (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-
25 naphthyl)anisole, which were purified by silica gel column eluting with AcOEt-Hexane(2 : 98 → 100 : 0) to yield the two isomers (totally 267 mg, 45% from 2):

- The first isomer, **compound 4**: GC-MS (R_t = 14.84 min) 401.15 (M⁺+1, 0.3%), 400.15 (M⁺, 0.9), 359.15 (0.6), 330.15 (0.4), 302.15 (3.2), 274.15 (8.0), 247.05 (23.0), 215.10
30 (12.7), 202.05 (7.8), 153.15 (100), 126.15 (10.1); δ_H (400 MHz, CDCl₃) 1.02 (d, J=6.4 Hz,

6H), 2.15 (dd, $J=11.2, 6.4$ Hz, 1H), 2.31 (dd, $J=11.2, 6.4$ Hz, 1H), 2.60 (m, 1H), 2.74 (dd, $J=11.2, 3.2$ Hz, 1H), 2.80 (dd, $J=11.2, 3.2$ Hz, 1H), 2.94 (dd, $J=13.6, 7.2$ Hz, 1H), 3.03 (dt, $J=6.4, 3.2$ Hz, 1H), 3.20 (dd, $J=13.6, 5.6$ Hz, 1H), 3.73 (s, 3H), 5.12 (m, 2H), 5.73 (brs, 1H), 5.83 (m, 1H), 6.68 (dd, $J=8.0, 2.4$ Hz, 1H), 7.00 (d, $J=8.0$ Hz, 1H), 7.12 (m, 2H), 7.42 (m, 3H), 7.62 (d, $J=7.2$ Hz, 1H), 7.71 (d, $J=8.0$ Hz, 1H), 7.80 (d, $J=8.0$ Hz, 1H), 8.28 (brs, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 13.2, 14.2, 35.6, 52.1, 53.0, 55.1, 55.2, 57.2, 63.8, 111.6, 114.4, 117.2, 121.1, 123.8, 125.2, 125.7, 125.8, 127.2, 127.5, 127.8, 128.9, 132.1, 134.0, 135.5, 137.4, 145.5, 159.5

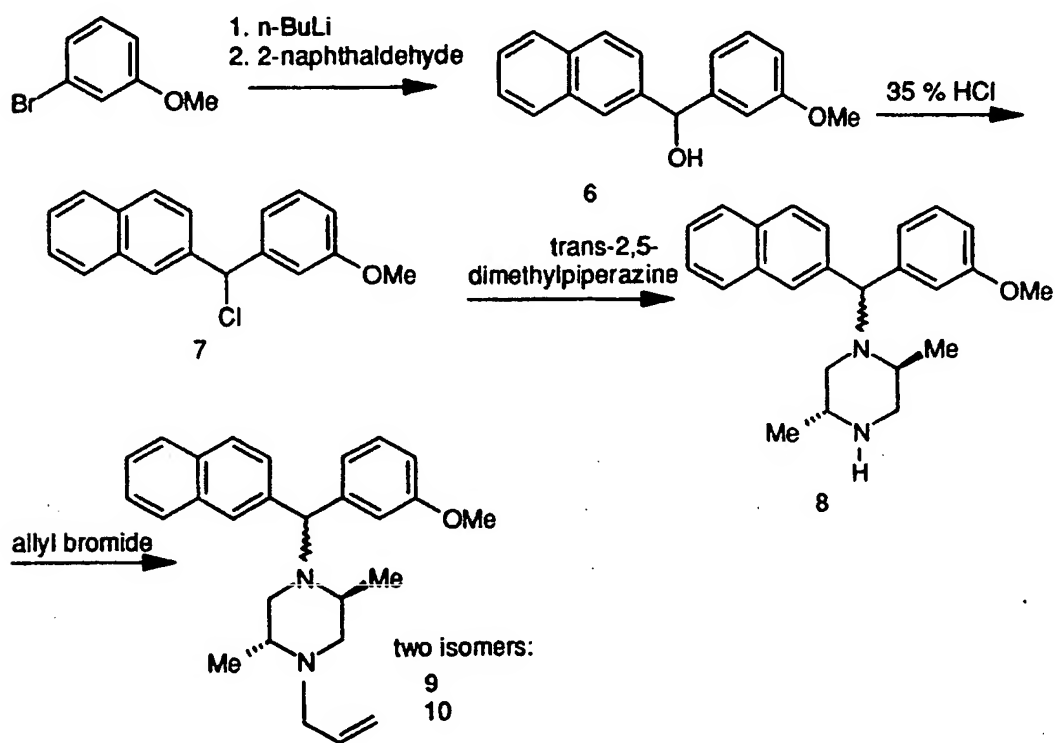
10 Its HCl salt: m.p. 124-135°C (Ether); ν_{max} (KBr) cm^{-1} 3483, 1601, 1264; *Anal.* Calcd. for $C_{27}H_{32}N_2O \cdot 2HCl \cdot 1.0H_2O$: C, 65.98; H, 7.38; N, 5.70. Found: C, 66.12; H, 7.25; N, 5.42.

The second isomer, **compound 5**: GC-MS ($R_t = 14.65$ min) 401.25 ($M^+ + 1$, 0.2%), 400.25 (M^+ , 0.8), 359.15 (0.4), 330.15 (0.4), 302.15 (3.1), 274.15 (8.0), 247.05 (21.7), 215.10 (13.0), 202.05 (7.0), 153.15 (100), 126.15 (9.7); δ_H (400 MHz, $CDCl_3$) 0.93 (d, $J=6.4$ Hz, 3H), 1.15 (d, $J=6.4$ Hz, 3H), 2.14 (m, 2H), 2.37 (m, 1H), 2.60 (dd, $J=11.6, 2.8$ Hz, 1H), 2.84 (m, 2H), 2.96 (m, 1H), 3.35 (dd, $J=13.2, 5.2$ Hz, 1H), 5.13 (m, 2H), 5.81 (s, 1H), 5.86 (m, 1H), 6.73 (dd, $J=8.0, 2.8$ Hz, 1H), 6.81 (s, 1H), 6.84 (d, $J=8.0$ Hz, 1H), 7.16 (m, 1H), 7.40 (m, 3H), 7.70 (m, 2H), 7.80 (d, $J=8.0$ Hz, 1H), 8.15 (d, $J=8.0$ Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.7, 16.3, 38.8, 53.6, 55.0, 55.6, 56.8, 59.3, 63.6, 111.5, 115.6, 117.4, 121.9, 124.6, 125.0, 125.1, 125.4, 126.2, 127.4, 128.5, 128.9, 131.6, 133.9, 135.0, 138.3, 142.2, 159.4.

25 Its HCl salt: m.p. 150.5-153°C (Ether); ν_{max} (KBr) cm^{-1} 3483, 1600, 1262; *Anal.* Calcd. for $C_{27}H_{32}N_2O \cdot 2HCl \cdot 0.75H_2O$: C, 66.59; H, 7.35; N, 5.75. Found: C, 66.41; H, 7.03; N, 5.48.

Scheme 2

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole
(9 & 10).



5

The compounds according to Examples 4-6 were synthesized as shown in Scheme 2 above.

10

B.**I. Preparation of 3-methoxy- α -(2-naphthyl)benzyl alcohol (compound 6)**

The compound 6 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 2-naphtaldehyde.

5

GC-MS (R_t = 10.68 min) 264 (M^+), 247, 231, 215, 202, 155, 135, 128, 109; δ_H (400 MHz, $CDCl_3$) 3.15 (brs, 1H), 3.59 (s, 3H), 5.71 (s, 1H), 6.69 (dd, $J=8.4, 2.8$ Hz, 1H), 6.87 (m, 2H), 7.11 (t, $J=8.0$ Hz, 1H), 7.29 (dd, $J=8.4, 1.2$ Hz, 1H), 7.35 (m, 2H), 7.63 (d, $J=8.4$ Hz, 1H), 7.70 (m, 3H); δ_{C-13} (100 MHz, $CDCl_3$) 55.0, 75.9, 112.1, 112.8, 118.9, 124.6, 10 124.9, 125.7, 125.9, 127.5, 127.9, 128.1, 129.3, 132.7, 133.1, 141.0, 145.2, 159.5.

II. Preparation of 3-methoxy- α -(2-naphthyl)benzyl chloride (compound 7)

15 The compound 7 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 6.

GC-MS (R_t = 10.58 min) 282 (M^+), 247, 231, 215, 202, 189, 151, 123, 101.

20 **Example 4**

Preparation of (\pm)-trans-1-(3-methoxy- α -(2-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 8)

25 The compound 8 was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 7.

Used directly in the next step: GC-MS (R_t = 14.03 min) 360 (M^+), 331, 301, 276, 247, 219, 169, 131, 113.

Example 5 and 6Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole (compounds 9 & 10)

- 5 The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 8.

Compound 9 (one pure isomer): GC-MS (R_t = 16.05 min) 401.25 (0.2%), 400.25 (0.8), 359.15 (0.4), 330.15 (0.4), 302.15 (3.1), 274.15 (8.0), 247.05 (21.7), 215.10 (13.0),
10 202.05 (7.0), 153.15 (100), 126.15 (9.7); δ_H (400 MHz, $CDCl_3$) 1.36 (d, $J=6.4$ Hz, 3H), 1.41 (d, $J=6.4$ Hz, 3H), 3.16 (dd, $J=13.2, 2.4$ Hz, 1H), 3.26 (d, $J=13.2$ Hz, 1H), 3.46 (m, 1H), 3.86 (s, 3H), 3.94 (dd, $J=11.2, 2.8$ Hz, 1H), 4.10 (m, 2H), 4.46 (m, 2H), 5.58 (m, 2H), 5.78 (s, 1H), 6.05 (m, 1H), 6.96 (dd, $J=8.0, 2.0$ Hz, 1H), 7.18 (s, 1H), 7.33 (m, 1H), 7.44 (m, 1H), 7.50 (m, 2H), 7.83 (m, 3H), 8.04 (d, $J=8.0$ Hz, 1H), 8.13 (s, 1H), 13.6 (brs,
15 2H).

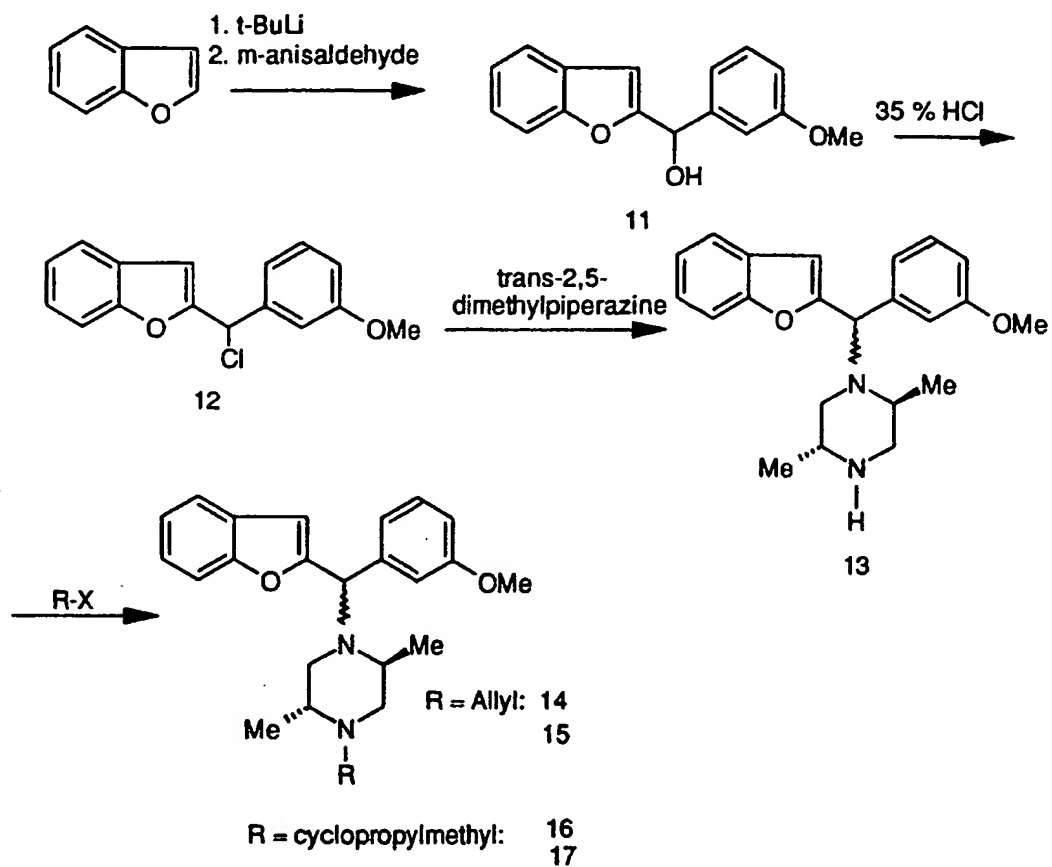
Its HCl salt: m.p. 129-138°C (Ether); ν_{max} (KBr) cm^{-1} 3426, 1600, 1262; *Anal.* Calcd. for $C_{27}H_{32}N_2O \cdot 2HCl \cdot 0.75H_2O$: C, 66.59; H, 7.35; N, 5.75. Found: C, 66.80; H, 7.11; N, 5.42.

20

Compound 10 (a mixture of two isomers) Its HCl salt: m.p. 160-162.5°C (Ether); ν_{max} (KBr) cm^{-1} 3380, 1600, 1261; *Anal.* Calcd. for $C_{27}H_{32}N_2O \cdot 2HCl \cdot 0.50H_2O$: C, 67.21; H, 7.31; N, 5.81. Found: C, 67.13; H, 6.97; N, 5.47.

Scheme 3

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (14, 15, 16 & 17).



5

The compounds according to Examples 7-11 were synthesized as shown in Scheme 3
10 above.

C**I. Preparation of 3-methoxy- α -(2-benzofuranyl)benzyl alcohol (compound 11)**

The compound of this Example was prepared by following the synthesis procedure as
5 described for Example 1.

GC-MS (R_t = 9.54 min) 254.15 (M^+ , 100%), 237.10 (73.8), 221.05 (19.6), 194.10 (17.8),
165.10 (30.3), 147.05 (76.7), 135.10 (69.2), 118.10 (35.4), 108.10 (26.5), 91.10 (47.1); δ_H
(400 MHz, $CDCl_3$) 3.21 (brs, 1H), 3.72 (s, 3H), 5.82 (s, 1H), 6.47 (s, 1H), 6.80-7.50 (m,
10 8H).

II. Preparation of 3-methoxy- α -(2-benzofuranyl)benzyl chloride (compound 12)

15 The compound 12 was prepared by following the synthesis procedure as described for
compound 2, but substituting compound 1 for compound 11..

GC-MS (R_t = 9.08 min) 272.05 (M^+ , 4.1%), 237.10 (100), 221.05 (4.5), 194.10 (14.7),
165.10 (23.1); δ_H (400 MHz, $CDCl_3$) 3.78 (s, 3H), 6.11 (s, 1H), 6.56 (s, 1H), 6.85-7.50
20 (m, 8H).

Example 7**Preparation of (\pm)-trans-1-(3-methoxy- α -(2'-benzofuranyl)benzyl)-2,5-
dimethylpiperazine (compound 13)**

25

The compound 13 was prepared by following the synthesis procedure as described for
compound 3, but substituting compound 2 for compound 12.

GC-MS (R_t = 11.87 min & R_t = 12.09 min) 351.15 (M^+ +1, 2.2%), 350.15 (M^+ , 8.6),
30 321.20 (0.4), 308.15 (0.2), 294.20 (18.3), 266.10 (58.6), 237.10 (100), 221.05 (3.0),

194.10 (10.0), 178.05 (4.1), 165.10 (13.0), 131.05 (2.9), 113.10 (43.8); δ_H (400 MHz, $CDCl_3$) (isomer at $R_t = 11.87$ min) 0.92 (d, $J=6.4$ Hz, 3H), 1.20 (d, $J=6.4$ Hz, 3H), 1.92 (dd, $J=11.2, 10.8$ Hz, 1H), 2.44 (m, 1H), 2.69 (dd, $J=11.2, 10.8$ Hz, 1H), 2.83 (m, 2H), 2.90 (m, 1H), 3.78 (s, 3H), 5.56 (s, 1H), 6.61 (s, 1H), 6.80 (d, $J=8.0$ Hz, 1H), 7.00 (d, $J=8.0$ Hz, 1H), 7.10 (s, 1H), 7.24 (m, 3H), 7.46 (d, $J=8.0$ Hz, 1H), 7.56 (d, $J=8.0$ Hz, 1H); (isomer at $R_t = 12.09$ min) 0.96 (d, $J=6.4$ Hz, 3H), 1.22 (d, $J=6.4$ Hz, 3H), 1.83 (dd, $J=11.2, 10.8$ Hz, 1H), 2.40 (m, 1H), 2.65 (m, 1H), 2.90 (m, 3H), 3.80 (s, 3H), 5.47 (s, 1H), 6.63 (s, 1H), 6.84 (m, 2H), 7.21 (m, 2H), 7.24 (m, 2H), 7.46 (d, $J=8.0$ Hz, 1H), 7.51 (d, $J=8.0$ Hz, 1H).

10

Its HCl salt: m.p. 115-125°C (Ether); ν_{max} (KBr) cm^{-1} 3373, 1595, 1257; *Anal.* Calcd. for $C_{22}H_{26}N_2O_2 \cdot 1.70HCl \cdot 0.20H_2O$: C, 63.51; H, 6.81; N, 6.73. Found: C, 63.60; H, 6.80; N, 6.70.

15 Example 8 and 9

Preparation of (\pm)-3-(($\alpha R^*/S^*$)- α -((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compounds 14 & 15)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 13..

The first isomer, compound 14: GC-MS ($R_t = 13.03$ min) 390.20 (M^+ , 1.5%), 349.15 (0.4), 320.10 (0.3), 292.10 (1.7), 264.10 (4.2), 237.10 (25.1), 221.05 (1.4), 194.10 (5.2), 165.10 (5.5), 153.15 (100), 126.15 (4.8), 98.05 (8.7), 84.10 (17.8); δ_H (400 MHz, $CDCl_3$) 0.97 (d, $J=6.4$ Hz, 3H), 1.21 (d, $J=6.4$ Hz, 3H), 2.12 (m, 2H), 2.35 (m, 1H), 2.65 (m, 1H), 2.75 (dd, $J=11.6, 2.4$ Hz, 1H), 2.81 (m, 3H), 3.42 (dd, $J=13.6, 5.2$ Hz, 1H), 3.78 (s, 3H), 5.14 (m, 2H), 5.51 (s, 1H), 5.85 (m, 1H), 6.61 (s, 1H), 6.81 (dd, $J=8.0, 2.4$ Hz, 1H), 7.01 (d, $J=8.0$ Hz, 1H), 7.11 (s, 1H), 7.24 (m, 3H), 7.44 (d, $J=8.0$ Hz, 1H), 7.54 (d, $J=8.0$ Hz, 1H); δ_C -13 (100 MHz, $CDCl_3$) 17.2, 17.5, 53.1, 54.4, 55.2, 56.0, 56.6, 59.2, 60.4, 106.8,

111.3, 112.1, 114.2, 117.8, 120.6, 120.7, 122.6, 123.8, 128.1, 129.0, 134.8, 141.4, 154.9, 155.2, 159.6.

Its HCl salt: m.p. 122-128°C (Ether); ν_{\max} (KBr) cm^{-1} 3490, 1602, 1253; *Anal.* Calcd. for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2 \cdot 2\text{HCl} \cdot 0.25\text{H}_2\text{O}$: C, 64.17; H, 7.00; N, 5.99. Found: C, 64.27; H, 6.92; N, 5.92.

The second isomer, **compound 15**: GC-MS ($R_t = 13.23$ min) 390.20 (M^+ , 3.1%), 349.15 (0.5), 292.10 (2.2), 264.10 (5.5), 237.10 (33.2), 221.05 (1.8), 194.10 (7.1), 165.10 (7.7), 153.15 (100), 126.15 (7.1), 98.15 (18.4), 84.10 (25.0); δ_H (400 MHz, CDCl_3) 1.00 (d, $J=6.4$ Hz, 3H), 1.21 (d, $J=6.4$ Hz, 3H), 2.12 (m, 2H), 2.48 (m, 1H), 2.61 (m, 1H), 2.78 (dd, $J=11.6, 2.4$ Hz, 1H), 2.83 (m, 3H), 3.42 (dd, $J=13.6, 5.6$ Hz, 1H), 3.79 (s, 3H), 5.15 (m, 2H), 5.40 (s, 1H), 5.85 (m, 1H), 6.64 (s, 1H), 6.86 (m, 3H), 7.20 (m, 3H), 7.44 (d, $J=8.0$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 1H).

15

Its HCl salt: m.p. 97-104°C (Ether); ν_{\max} (KBr) cm^{-1} 3438, 1601 (s), 1260; *Anal.* Calcd. for $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2 \cdot 2\text{HCl} \cdot 0.50\text{H}_2\text{O}$: C, 63.56; H, 7.04; N, 5.93. Found: C, 63.70; H, 6.68; N, 5.83.

20 Example 10 and 11

Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compounds 16 & 17)

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, except using cyclopropyl methyl iodide and substituting compound 3 for compound 13.

The first isomer, **compound 16**: GC-MS ($R_t = 14.87$ min) 405.25 ($M^+ + 1$, 2.3%), 404.25 (M^+ , 8.2), 362.20 (0.5), 349.15 (0.4), 320.20 (0.8), 292.20 (4.1), 291.10 (3.4), 265.10 (16.5), 237.10 (65.9), 194.10 (11.5), 167.20 (100), 140.20 (3.9), 124.15 (4.6), 98.15

30

(44.0); δ_{H} (400 MHz, CDCl_3) 0.05 (m, 2H), 0.46 (m, 2H), 0.80 (m, 1H), 0.92 (d, $J=6.0$ Hz, 3H), 1.21 (d, $J=6.0$ Hz, 3H), 2.01 (dd, $J=12.8, 7.2$ Hz, 1H), 2.17 (m, 2H), 2.35 (m, 1H), 2.64 (dd, $J=13.2, 6.4$ Hz, 1H), 2.66 (m, 1H), 2.72 (dd, $J=12.0, 2.4$ Hz, 1H), 3.04 (dd, $J=11.2, 3.2$ Hz, 1H), 3.75 (s, 3H), 5.50 (s, 1H), 6.58 (s, 1H), 6.79 (dd, $J=8.0, 2.4$ Hz, 1H), 7.01 (d, $J=8.0$ Hz, 1H), 7.09 (s, 1H), 7.20 (m, 3H), 7.41 (d, $J=8.0$ Hz, 1H), 7.51 (m, 1H); $\delta_{\text{C-13}}$ (100 MHz, CDCl_3) 3.2, 4.7, 7.4, 17.4, 17.7, 53.1, 54.5, 55.2, 56.0, 58.3, 59.2, 60.8, 106.8, 111.3, 112.0, 114.2, 120.6, 120.7, 122.6, 123.7, 128.0, 129.0, 141.4, 154.8, 155.2, 159.6.

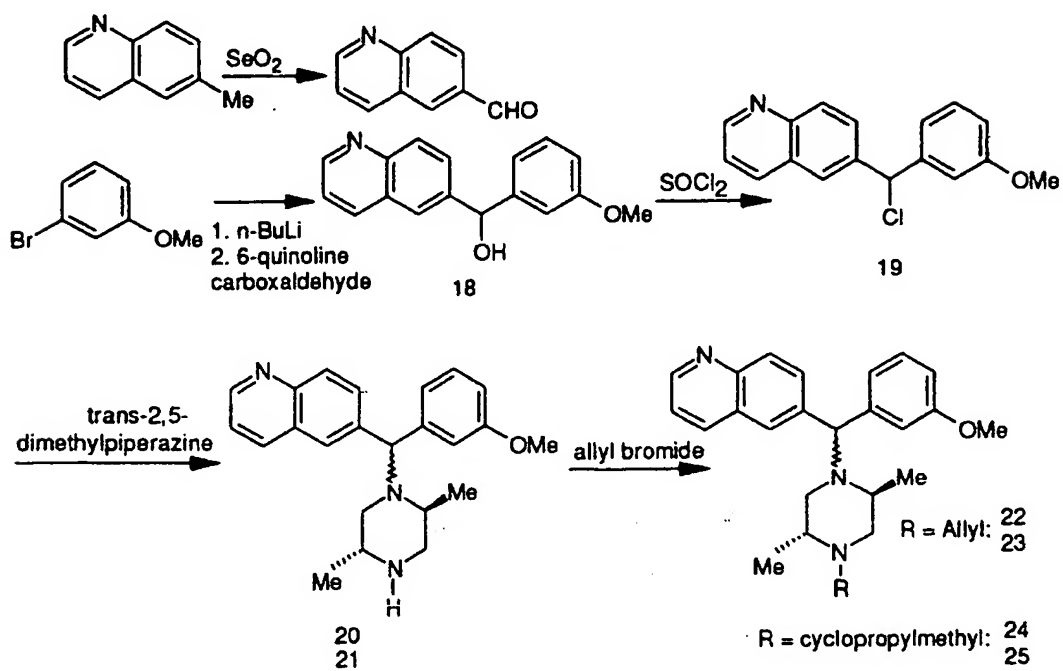
10 Its HCl salt: m.p. 162-164°C (Ether); ν_{max} (KBr) cm^{-1} 3414, 1599, 1255; *Anal.* Calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 64.19; H, 7.25; N, 5.76. Found: C, 64.43; H, 7.30; N, 5.78.

The second isomer, **compound 17**: GC-MS ($R_t = 15.17$ min) 405.25 (M^++1 , 2.2%), 404.25 (M^+ , 8.9), 362.10 (0.6), 349.15 (0.4), 320.10 (0.8), 292.10 (5.0), 291.10 (3.9), 265.10 (19.4), 237.10 (72.2), 194.10 (12.8), 167.20 (100), 140.10 (3.9), 124.15 (4.8), 98.15 (45.5); δ_{H} (400 MHz, CDCl_3) 0.08 (m, 2H), 0.48 (m, 2H), 0.82 (m, 1H), 0.97 (d, $J=6.4$ Hz, 3H), 1.25 (d, $J=6.4$ Hz, 3H), 2.10 (m, 2H), 2.28 (dd, $J=11.2, 10.0$ Hz, 1H), 2.49 (m, 1H), 2.62 (dd, $J=13.2, 6.0$ Hz, 1H), 2.63 (m, 1H), 2.83 (dd, $J=11.2, 2.8$ Hz, 1H), 3.02 (dd, $J=11.2, 3.2$ Hz, 1H), 3.78 (s, 3H), 5.43 (s, 1H), 6.64 (s, 1H), 6.87 (m, 3H), 7.21 (m, 3H), 7.45 (dd, $J=7.6, 1.2$ Hz, 1H), 7.50 (m, 1H); $\delta_{\text{C-13}}$ (100 MHz, CDCl_3) 3.3, 4.6, 7.4, 17.0, 17.6, 52.6, 55.2, 55.4, 55.6, 58.3, 60.3, 61.6, 105.7, 111.3, 112.5, 115.9, 120.5, 122.1, 112.5, 123.5, 128.4, 128.9, 137.3, 155.0, 158.3, 159.3.

25 Its HCl salt: m.p. 92-105°C (Ether); ν_{max} (KBr) cm^{-1} 3398, 1599, 1257; *Anal.* Calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_2 \cdot 2\text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 64.19; H, 7.25; N, 5.76. Found: C, 64.38; H, 7.14; N, 5.73.

Scheme 4

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (22, 23, 24 & 25).



D.**I. Preparation of 6-Quinolinecarboxaldehyde**

5 A mixture of 6-methylquinoline (5.72 g, 40.0 mmol) and selenium oxide (4.44 g, 40.0 mmol) was heated to 220°C for 1h. After cooling down the residue was dissolved in ethyl acetate (100 mL). The organic solution was washed with brine, dried over MgSO₄. Evaporation of solvents provided a solid, which was recrystallized from ether-hexane (1 : 1) mixture to give 6-quinolinecarboxaldehyde (3.45 g, 55%).

10

GC-MS (R_t = 5.29 min) 157.15 (M^+ , 100%), 156.15 (92.2), 128.15 (62.9), 101.15 (16.0); δ_H (400 MHz, CDCl₃) 7.53 (m, 1H), 8.21 (m, 2H), 8.33 (m, 2H), 9.06 (m, 1H), 10.21 (s, 1H); δ_{C-13} (100 MHz, CDCl₃) 122.1, 126.6, 127.6, 130.7, 133.5, 134.2, 137.3, 150.8, 153.0, 191.3.

15

The compounds according to Examples 12-17 were synthesized as shown in Scheme 4 above.

II. Preparation of 3-methoxy- α -(6-quinolinyl)benzyl alcohol (compound 18)

20

The compound 18 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 6-quinolinecarboxaldehyde.

GC-MS (R_t = 11.13 min) 265.10 (M^+ , 49.0%), 248.05 (2.3), 204.05 (9.7), 156.05 (37.6),
25 135.00 (100), 109.00 (43.5); δ_H (400 MHz, CDCl₃) 3.73 (s, 3H), 5.94 (s, 1H), 6.78 (d, J =8.4 Hz, 1H), 6.95 (m, 2H), 7.22 (m, 1H), 7.31 (m, 1H), 7.61 (d, J =8.4 Hz, 1H), 7.83 (s, 1H), 7.95 (d, J =8.4 Hz, 1H), 8.07 (d, J =8.0 Hz, 1H), 8.73 (m, 1H); δ_{C-13} (100 MHz, CDCl₃) 55.2, 75.7, 112.3, 113.1, 119.1, 121.2, 124.6, 128.5, 129.4, 129.6, 136.3, 142.1, 145.2, 147.6, 150.1, 159.8.

III. Preparation of 3-methoxy- α -(6-quinolinyl)benzyl chloride (compound 19)

The compound 19 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 18.

Used directly in the next step: δ_H (400 MHz, $CDCl_3$) 3.73 (s, 3H), 5.98 (s, 1H), 6.8-8.2 (m, 9H), 8.80 (s, 1H).

Example 12 and 13

Preparation of (\pm)-trans-1-(3-methoxy- α -(6'-quinolinyl)benzyl)-2,5-dimethylpiperazine (compounds 20 & 21)

The compounds of these Examples were prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 19.

GC-MS (R_t = 14.91 min) 361.20 (M^+ , 0.8%), 332.15 (0.3), 306.15 (0.6), 302.15 (14.4), 277.15 (52.5), 248.05 (100), 233.00 (10.6), 204.05 (17.1), 176.05 (2.7), 151.05 (1.4), 142.10 (1.8), 113.10 (19.9).

The first isomer, compound 20: δ_H (400 MHz, $CDCl_3$) 1.06 (d, $J=6.4$ Hz, 3H), 1.24 (d, $J=6.4$ Hz, 3H), 1.84 (dd, $J=11.6, 9.2$ Hz, 1H), 2.60 (m, 2H), 2.77 (m, 2H), 3.06 (m, 2H), 3.80 (s, 3H), 5.44 (s, 1H), 6.77 (s, 1H), 6.83 (d, $J=8.0$ Hz, 1H), 6.88 (dd, $J=8.0, 2.4$ Hz, 1H), 7.31 (m, 1H), 7.37 (m, 1H), 7.82 (s, 1H), 7.84 (m, 1H), 8.03 (d, $J=8.8$ Hz, 1H), 8.09 (d, $J=8.8$ Hz, 1H), 8.87 (m, 1H).

Compound 21 (a mixture of two isomers, ~25% **compound 20**): δ_{H} (400 MHz, CDCl_3) 1.20 (m, 6H), 2.05 (m, 1H), 2.73 (m, 2H), 2.87 (m, 1H), 3.13 (m, 2H), 3.73 & 3.76 (s, 3H), 5.38 (s, 1H), 6.38 (brs, NH), 6.70-8.15 (m, 9H), 8.84 (m, 1H).

5 **Example 14**

Preparation of (\pm)-3-(($\alpha\text{R}^*/\text{S}^*$)- α -(2 S^* ,5 R^*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 22)

The compound of this Example was prepared by following the synthesis procedure as
10 described for Examples 2 and 3, but substituting compound 3 for compound 20.

GC-MS ($R_t = 17.22$ min) 401.25 (M^+ , 0.3%), 360.20 (0.3), 331.10 (0.2), 303.20 (1.7), 276.10 (4.5), 248.10 (17.2), 233.10 (4.5), 204.10 (8.0), 176.10 (1.3), 153.20 (100), 126.20 (5.4); δ_{H} (400 MHz, CDCl_3) 1.0 (d, $J=6.4$ Hz, 3H), 1.21 (d, $J=6.4$ Hz, 3H), 1.99 (m, 1H),
15 2.20 (m, 1H), 2.56 (m, 1H), 2.66 (m, 1H), 2.71 (m, 1H), 2.85 (m, 1H), 2.90 (m, 1H), 3.37 (dd, $J=13.2, 4.0$ Hz, 1H), 3.78 (s, 3H), 5.17 (m, 2H), 5.35 (s, 1H), 5.87 (m, 1H), 6.82 (m, 3H), 7.26 (t, $J=7.6$ Hz, 1H), 7.36 (m, 1H), 7.81 (s, 1H), 7.88 (d, $J=8.8$ Hz, 1H), 8.03 (d, $J=8.8$ Hz, 1H), 8.09 (d, $J=7.6$ Hz, 1H), 8.87 (m, 1H); $\delta_{\text{C-13}}$ (100 MHz, CDCl_3) 15.7, 16.4, 52.0, 53.7, 55.2, 55.5, 56.8, 58.9, 65.9, 112.1, 116.3, 117.8, 120.9, 122.5, 126.5, 127.9,
20 128.9, 129.0, 130.2, 134.8, 136.0, 139.2, 141.1, 147.6, 150.0, 159.5.

Its HCl salt: m.p. 128-140°C (Ether); ν_{max} (KBr) cm^{-1} 3376, 1596, 1263; *Anal.* Calcd. for $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O} \cdot 2.30\text{HCl} \cdot 0.1\text{H}_2\text{O}$: C, 64.10; H, 6.93; N, 8.62. Found: C, 64.08; H, 6.92; N, 8.35.

Example 15**Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 23)**

- 5 The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 21.

GC-MS (R_t = 17.21 min) 401.35 (M^+ , 0.4%), 360.30 (0.2), 331.20 (0.2), 303.20 (1.6), 276.10 (4.8), 248.10 (17.3), 233.10 (4.4), 204.10 (8.1), 176.10 (1.3), 153.20 (100), 126.20 (5.6); δ_H (400 MHz, $CDCl_3$) 1.01 (d, $J=6.0$ Hz, 3H), 1.21 (d, $J=6.0$ Hz, 3H), 1.95 (m, 1H), 2.16 (m, 1H), 2.56 (m, 1H), 2.66 (m, 1H), 2.74 (m, 1H), 2.80 (m, 1H), 2.87 (m, 1H), 3.30 (dd, $J=13.6, 5.6$ Hz, 1H), 3.77 (s, 3H), 5.13 (m, 2H), 5.34 (s, 1H), 5.82 (m, 1H), 6.77 (dd, $J=8.0, 2.4$ Hz, 1H), 6.99 (d, $J=7.6$ Hz, 1H), 7.11 (s, 1H), 7.21 (d, $J=8.0$ Hz, 1H), 7.38 (dd, $J=8.4, 4.0$ Hz, 1H), 7.59 (d, $J=8.4$ Hz, 1H), 7.66 (s, 1H), 8.03 (d, $J=8.8$ Hz, 1H), 8.11 (d, $J=8.4$ Hz, 1H), 8.88 (m, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.3, 16.2, 51.9, 53.4, 55.2, 55.3, 56.8, 58.5, 66.1, 111.8, 114.0, 117.6, 120.6, 121.1, 127.9, 128.3, 128.9, 129.1, 131.4, 134.9, 136.0, 137.1, 144.1, 147.7, 150.2, 159.6.

Its HCl salt: m.p. 177-182°C (Ether); ν_{max} (KBr) cm^{-1} 3405, 1597, 1260; *Anal.* Calcd. for $C_{26}H_{31}N_3O \cdot 0.80HCl$: C, 62.01; H, 6.76; N, 8.34. Found: C, 61.98; H, 6.77; N, 8.03.

Example 16 and 17**Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compounds 24 & 25)**

25

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting allylbromide for cyclopropylmethyliodide..

The first isomer, compound 24: GC-MS (R_t = 20.77 min) 415.25 (M^+ , 3.8%), 344.15 (2.4), 302.10 (9.5), 276.10 (58.8), 248.15 (79.1), 233.10 (17.2), 204.10 (29.4), 176.10

30

(4.2), 167.15 (100), 138.15 (14.2), 112.15 (47.0); δ_{H} (400 MHz, CDCl_3) 0.10 (m, 2H), 0.51 (m, 2H), 0.86 (m, 1H), 0.97 (d, $J=6.4$ Hz, 3H), 1.25 (d, $J=6.4$ Hz, 3H), 1.98 (dd, $J=11.2$, 8.8 Hz, 1H), 2.14 (dd, $J=13.2$, 6.4 Hz, 1H), 2.32 (dd, $J=10.8$, 5.6 Hz, 1H), 2.58 (m, 2H), 2.66 (dd, $J=11.6$, 2.8 Hz, 1H), 2.73 (m, 1H), 3.07 (dd, $J=11.2$, 3.2 Hz, 1H), 3.78 (s, 3H), 5.39 (s, 1H), 6.79 (s, 1H), 6.84 (m, 2H), 7.26 (t, $J=8.0$ Hz, 1H), 7.35 (dd, $J=8.4$, 4.0 Hz, 1H), 7.83 (s, 1H), 7.89 (d, $J=8.8$ Hz, 1H), 8.03 (d, $J=9.2$ Hz, 1H), 8.09 (d, $J=8.0$ Hz, 1H), 8.86 (dd, $J=4.0$, 2.0 Hz, 1H); $\delta_{\text{C-13}}$ (100 MHz, CDCl_3) 3.4, 4.4, 7.6, 16.2, 16.9, 52.1, 53.8, 55.2, 55.6, 58.5, 59.7, 65.6, 112.0, 116.3, 120.9, 122.6, 126.5, 127.9, 128.8, 129.0, 130.2, 136.0, 139.1, 141.1, 147.6, 149.9, 159.4.

10

Its HCl salt: m.p. 127-157°C (Ether); ν_{max} (KBr) cm^{-1} 3402, 1596, 1262; *Anal.* Calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O} \cdot 0.3\text{HCl} \cdot 0.75\text{H}_2\text{O}$: C, 60.23; H, 7.02; N, 7.80. Found: C, 60.49; H, 7.00; N, 7.73.

15

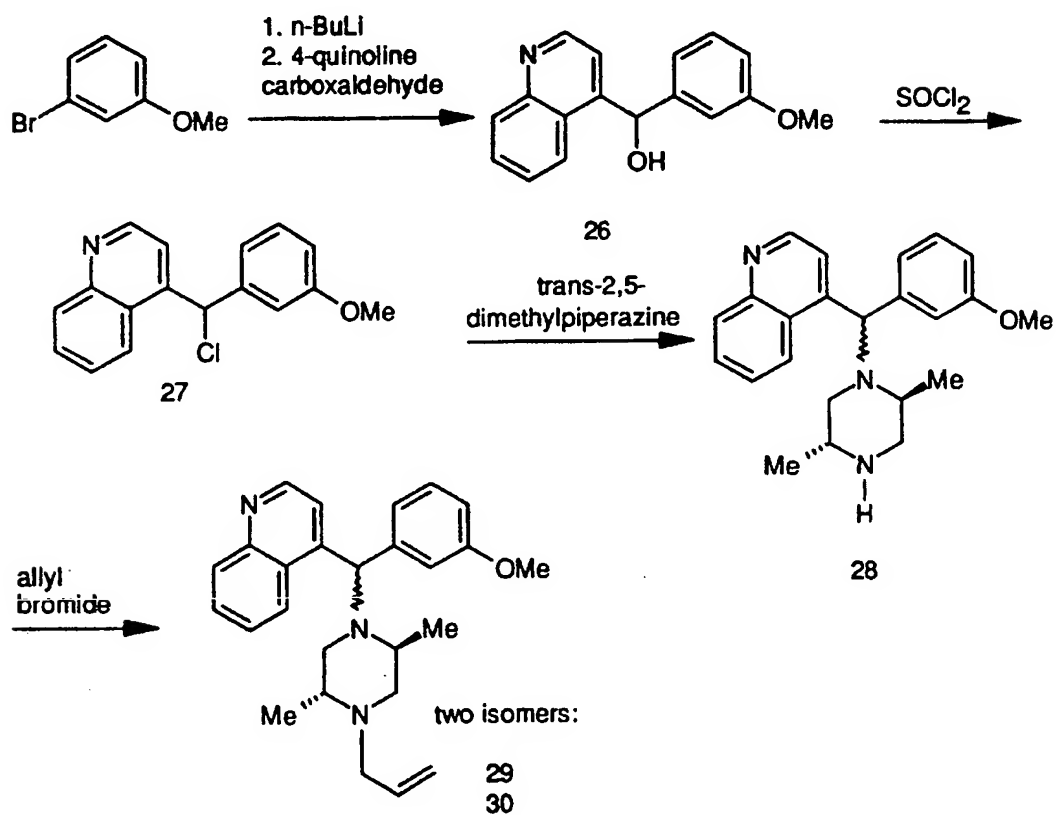
The second isomer, **compound 25**: GC-MS ($R_t = 20.73$ min) 415.25 (M^+ , 3.2%), 344.05 (2.3), 302.10 (7.7), 276.10 (48.5), 248.15 (69.6), 233.10 (15.7), 204.10 (25.8), 176.10 (3.7), 167.15 (100), 138.15 (12.2), 112.15 (46.8); δ_{H} (400 MHz, CDCl_3) 0.17 (m, 2H), 0.56 (m, 2H), 0.97 (m, 1H), 1.11 (brs, 3H), 1.27 (brs, 3H), 2.24 (m, 1H), 2.38 (m, 1H), 2.51 (m, 1H), 2.61 (m, 1H), 2.87 (m, 3H), 3.13 (m, 1H), 3.77 (s, 3H), 5.34 (s, 1H), 6.78 (d, $J=8.0$ Hz, 1H), 6.98 (d, $J=8.0$ Hz, 1H), 7.08 (s, 1H), 7.22 (t, $J=8.0$ Hz, 1H), 7.39 (dd, $J=8.4$, 4.4 Hz, 1H), 7.60 (d, $J=8.4$ Hz, 1H), 7.73 (s, 1H), 8.04 (d, $J=8.8$ Hz, 1H), 8.16 (d, $J=8.4$ Hz, 1H), 8.89 (d, $J=4.0$ Hz, 1H); $\delta_{\text{C-13}}$ (100 MHz, CDCl_3) 4.07, 4.37, 6.9, 14.8, 15.1, 51.4, 55.2, 56.2, 58.2, 60.3, 66.4, 111.8, 114.2, 120.6, 121.2, 128.0, 128.1, 129.2, 131.0, 136.0, 137.0, 143.8, 147.7, 150.3, 159.6.

25

Its HCl salt: m.p. 92-105°C (Ether); ν_{max} (KBr) cm^{-1} 3345, 1596, 1259.

Scheme 5

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Alkyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (29 & 30)



5

The compounds according to Examples 18-20 were synthesized as shown in Scheme 5
10 above.

E.**I. Preparation of 3-methoxy- α -(4-quinolinyl)benzyl alcohol (compound 26)**

- 5 The compound 26 was prepared by following the synthesis procedure as described for compound 1, but substituting 1-naphtaldehyde for 4-quinolinecarboxaldehyde..

GC-MS (R_t = 10.81 min) 266.10 ($M^+ + 1$, 11.8%), 265.10 (M^+ , 61.0), 248.05 (6.1), 232.00 (6.2), 216.05 (4.7), 204.00 (10.5), 191.05 (2.0), 176.00 (3.8), 156.00 (13.9), 135.10 (100),
10 129.10 (86.6), 109.10 (68.2), 102.10 (25.5); δ_H (400 MHz, $CDCl_3$) 3.67 (s, 3H), 5.30 (brs, 1H), 6.41 (s, 1H), 6.76 (d, $J=7.2$ Hz, 1H), 6.90 (m, 2H), 7.18 (t, $J=7.6$ Hz, 1H), 7.38 (m, 1H), 7.56 (t, $J=7.6$ Hz, 1H), 7.62 (m, 1H), 7.92 (d, $J=8.4$ Hz, 1H), 8.00 (d, $J=8.4$ Hz, 1H), 8.64 (dd, $J=4.4, 1.2$ Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 55.1, 72.1, 113.0, 113.2, 118.5, 119.5, 123.9, 125.7, 126.5, 129.0, 129.5, 129.7, 143.8, 147.8, 149.1, 149.9, 159.7.

II. Preparation of 3-methoxy- α -(4-quinolinyl)benzyl chloride (compound 27)

The compound 27 was prepared by following the synthesis procedure as described for
5 compound 2, but substituting compound 1 for compound 26.

Used directly in the next step: GC-MS (R_t = 10.54 min) 285.10 (M^+ +2, 11.5%), 283.10
(M^+ , 33.10), 268.05 (0.2), 248.15 (100), 233.10 (37.0), 217.05 (27.2), 204.10 (45.5),
178.10 (5.9), 176.10 (11.5), 151.10 (5.7), 139.05 (2.1), 108.60 (11.0), 102.10 (17.4).

10

Example 18

Preparation of (\pm)-trans-1-(3-methoxy- α -(4-quinolinyl)benzyl)-2,5-dimethyl- piperazine (compound 28)

15 The compound of this Example was prepared by following the synthesis procedure as
described for compound 3, but substituting compound 2 for compound 27.

GC-MS (R_t = 13.96 min) 362.20 (M^+ +1, 1.4%), 361.20 (M^+ , 6.6), 306.10 (2.0), 302.15
(18.3), 277.15 (59.6), 248.15 (100), 233.10 (15.8), 204.10 (20.9), 176.10 (3.8), 151.00
20 (1.8), 143.15 (1.4), 113.15 (15.8); δ_H (400 MHz, $CDCl_3$) 0.92 (d, J =6.4 Hz, 3H), 1.12 (d,
 J =6.4 Hz, 3H), 1.82 (dd, J =11.6, 10.0 Hz, 1H), 2.52 (brs, 1H), 2.62 (dd, J =11.6, 2.8 Hz,
1H), 2.72 (m, 1H), 2.77 (m, 1H), 2.88 (m, 1H), 2.98 (dd, J =11.6, 2.0 Hz, 1H), 3.72 (s,
3H), 5.86 (s, 1H), 6.69 (s, 1H), 6.72 (d, J =8.0, 1H), 6.78 (dd, J =8.0, 2.4 Hz, 1H), 7.20 (t,
 J =8.0 Hz, 1H), 7.37 (t, J =8.0 Hz, 1H), 7.60 (t, J =8.0 Hz, 1H), 7.65 (d, J =4.4 Hz, 1H), 7.99
25 (d, J =8.8 Hz, 1H), 8.09 (d, J =8.0 Hz, 1H), 8.89 (d, J =4.4 Hz, 1H).

Example 19 and 20Preparation of (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (compounds 29 & 30)

5

The compounds of these Examples were prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 28.

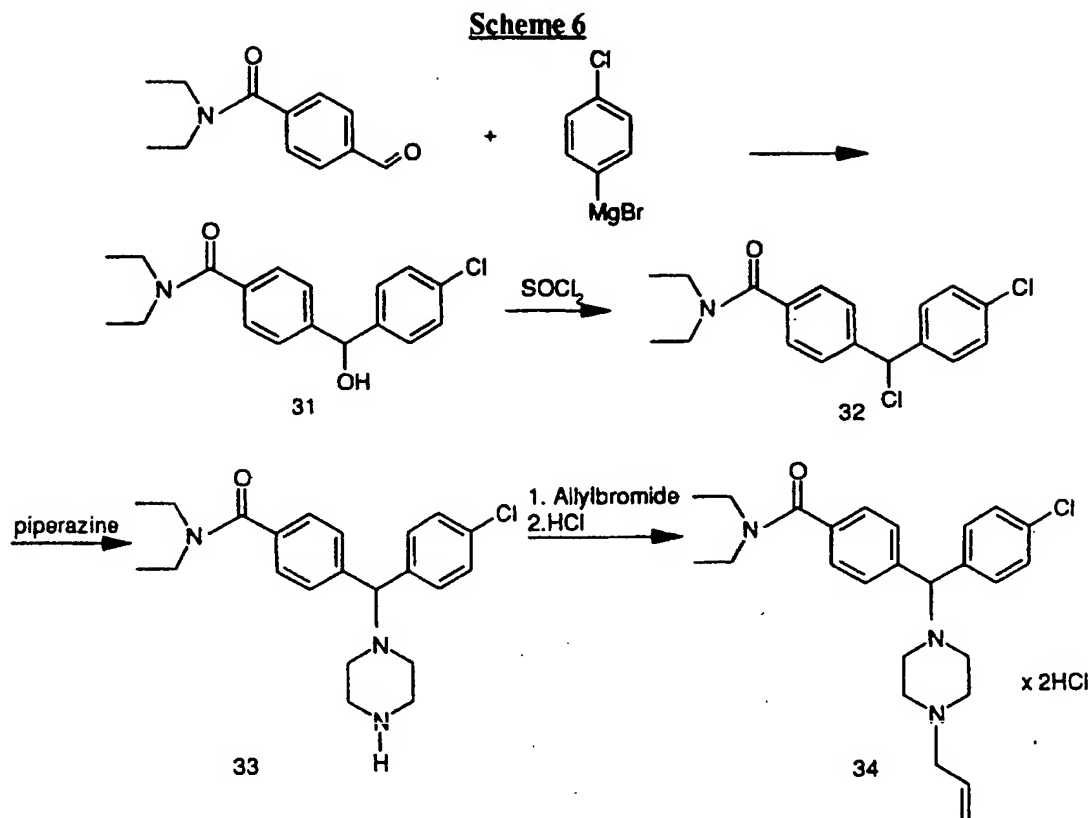
The first isomer, **compound 29**: GC-MS (R_t = 15.97 min) 401.15 (M^+ , 0.8%), 360.20 (0.8), 303.15 (3.3), 276.15 (5.7), 248.05 (15.3), 217.05 (6.3), 204.10 (10.4), 176.00 (2.2), 153.20 (100), 126.10 (5.3), 98.10 (13.8); δ_H (400 MHz, $CDCl_3$) 0.96 (d, $J=6.0$ Hz, 3H), 1.14 (d, $J=6.0$ Hz, 3H), 2.01 (m, 1H), 2.16 (t, $J=10.0$ Hz, 1H), 2.47 (m, 1H), 2.59 (d, $J=11.2$ Hz, 1H), 2.86 (m, 2H), 2.95 (t, $J=6.0$ Hz, 1H), 3.36 (dd, $J=13.6, 4.4$ Hz, 1H), 3.72 (s, 3H), 5.15 (m, 2H), 5.77 (s, 1H), 5.85 (m, 1H), 6.74 (m, 3H), 7.17 (t, $J=7.6$ Hz, 1H), 7.38 (t, $J=8.0$ Hz, 1H), 7.60 (dd, $J=7.2, 0.8$ Hz, 1H), 7.73 (d, $J=4.4$ Hz, 1H), 8.00 (d, $J=8.4$ Hz, 1H), 8.08 (d, $J=8.8$ Hz, 1H), 8.90 (d, $J=3.6$ Hz, 1H); δ_{C-13} (100 MHz, $CDCl_3$) 15.9, 16.6, 53.8, 55.1, 55.5, 56.7, 59.4, 63.2, 112.0, 115.7, 117.7, 120.6, 121.9, 124.4, 126.0, 126.8, 128.6, 129.3, 130.1, 134.8, 140.3, 148.5, 148.6, 150.2, 159.5.

Its HCl salt: m.p. 158-166°C (AcOEt-Ether); ν_{max} (KBr) cm^{-1} 3400, 1596, 1263; *Anal.* Calcd. for $C_{26}H_{31}N_3O \cdot 3.0HCl \cdot 0.9H_2O$: C, 59.24; H, 6.85; N, 7.97. Found: C, 59.31; H, 6.94; N, 7.80.

The second isomer, **compound 30**: GC-MS (R_t = 16.19 min) 401.25 (M^+ , 0.5%), 386.20 (0.2), 360.20 (0.7), 331.10 (0.3), 303.15 (3.3), 276.15 (4.7), 248.15 (13.7), 233.10 (5.8), 217.05 (4.9), 204.10 (9.8), 176.10 (1.8), 153.20 (100), 126.20 (5.2), 98.10 (13.9); δ_H (400 MHz, $CDCl_3$); δ_{C-13} (100 MHz, $CDCl_3$).

Its HCl salt: m.p. 155-165°C (AcOEt-Ether).

30



5

The compounds according to Examples 21-22 were synthesized as shown in Scheme 6 above.

10

E

I. Preparation of (±) 4-((α-Hydroxy)-4-chlorobenzyl)-N,N-diethylbenzamide (compound 31)

15 4-Formyl-N,N-diethylbenzamide (2.088 g, 10.1 mmol) was dissolved in 45 ml of anhydrous THF. The solution was cooled down to -78°C , followed by a dropwise addition of 10.1 ml

(10.1 mmol) of a 1.0 M solution of 4-Chloro-phenylmagnesium bromide in ether. The mixture was warmed up to room temperature within 3 hours. Then 50 ml of a saturated NH_4Cl -solution was added and the mixture was extracted with ethyl acetate (3x30 ml). The combined organic layers were washed with water (2 x 30 ml) and brine (1 x 30 ml), dried
5 (Na_2SO_4), filtered and the solvent was removed in *vacuo*. The residue was chromatographed on silica gel eluting with methanol:dichloromethane (1:125 - 3:125) to yield the title compound as a colorless oil.

10 ν_{max} (KBr)/ cm^{-1} 3329, 2977, 1595, 1461, 1289, 1094, 1051, 830; δ_{H} (400 MHz, CDCl_3) 1.09 (3H, br s), 1.21 (3H, br s), 3.22 (2H, br s), 3.33 (1H, d, J 3), 3.50 (2H, br s), 5.74 (1H, d, J 3), 7.22-7.34 (m, 8H);

15 **II. Preparation of (\pm) 4-((α -Chloro)-4-chlorobenzyl)-N,N-diethylbenzamide (compound 32)**

The compound 32 was prepared by following the synthesis procedure as described for compound 2, but substituting compound 1 for compound 31.

20 Used for the next step without further purification.

Example 21

Preparation of (\pm) 4-((α -(1-Piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide (compound 33)

25

The compound of this Example was prepared by following the synthesis procedure as described for compound 3, but substituting compound 2 for compound 32.

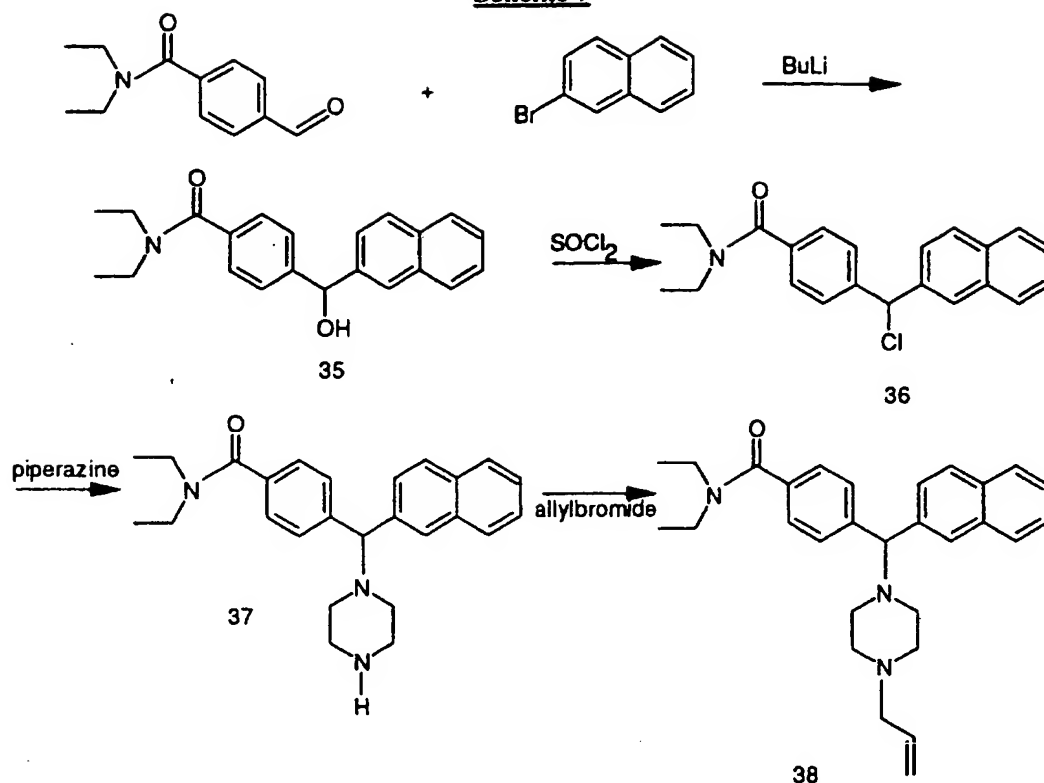
m.p. 112-113°C (from acetonitrile), ν_{\max} (KBr)/cm⁻¹ 3347, 2947, 2809, 1615, 1451, 1318, 1284, 1094, 836; δ_{H} (400 MHz, CDCl₃) 1.10 (3H, br s), 1.21 (3H, br s), 1.69 (1H, br s), 2.33 (4H, br s), 2.86-2.89 (4H, m), 3.24 (2H, br s), 3.51 (2H, br s), 4.22 (1H, s), 7.23-7.41 (8H, m); C₂₂H₂₈N₃OCl • 0.3 H₂O requires:
5 C: 67.52 H: 7.37 N: 10.74 Found: C: 67.68 H: 7.37 N: 10.73.

Example 22

Preparation of (±) 4-((α-(4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N-
10 diethylbenzamide • 2HCl (compound 34)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 33.

15 m.p. 147-163°C (from ether), ν_{\max} (KBr)/cm⁻¹ 3418, 2974, 2355, 1626, 1435, 1286, 1092, 945, 812; δ_{H} (400 MHz, CDCl₃) 1.06 (3H, br s), 1.19 (3H, br s), 3.0-3.7 (14H, m), 5.4-5.6 (2H, m), 6.0-6.2 (1H, br m), 7.2-7.8 (9H, m); C₂₅H₃₄N₃OCl₃ requires:
C: 60.18 H: 6.87 N: 8.42 Found: C: 60.48 H: 6.89 N: 8.31.

Scheme 7

5

The compounds according to Examples 23-24 were synthesized as shown in Scheme 7 above.

G

10 **I. Preparation of (±) 4-((α-Hydroxy)-2-naphthylmethyl)-N,N-diethylbenzamide (compound 35)**

The compound 35 was prepared by following the synthesis procedure as described for compound 1, but substituting 3-bromoanisole for 2-bromoanisole, and 1-naphtaldehyde for

15 N,N-diethyl-4-carboxybenzamide..

ν_{\max} (KBr)/ cm^{-1} 3302, 2976, 1607, 1430, 1290, 1098, 813; δ_{H} (400 MHz, CDCl_3) 1.09 (3H, br s), 1.22 (3H, br s), 2.60 (1H, d, J 3), 3.24 (2H, br s), 3.52 (2H, br s), 6.00 (1H, d, J 3), 7.30-7.50 (7H, m), 7.76-7.88 (4H, m);

5

II. Preparation of (\pm) 4-((α -Chloro)-2-naphtyl-methyl)-N,N-diethylbenzamide (compound 36)

The compound 36 was prepared by following the synthesis procedure as described for
10 compound 2, but substituting compound 1 for compound 35.

Used for the next step without further purification.

Example 23

15 **Preparation of (\pm) 4-((α -(1-Piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 37)**

The compound of this Example was prepared by following the synthesis procedure as described for Example 1, but substituting compound 2 for compound 36.

20

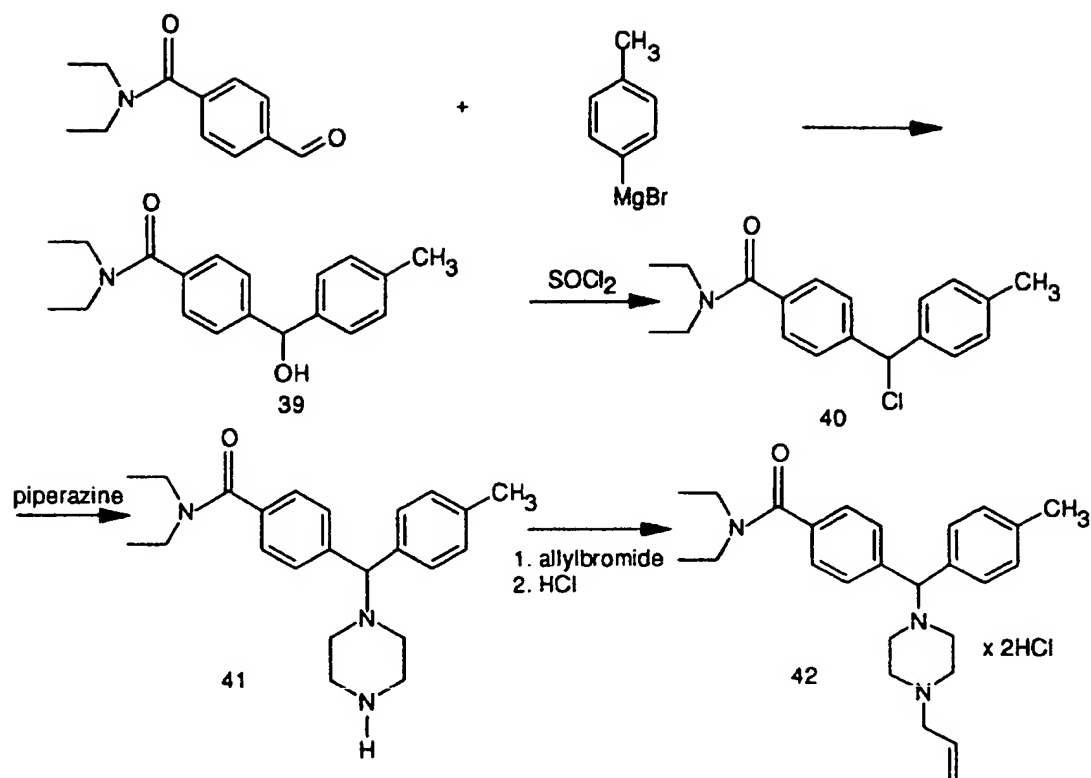
m.p. 106-108°C (from acetonitrile), ν_{\max} (KBr)/ cm^{-1} 3324, 3052, 2964, 2810, 2774, 1613, 1465, 1287, 1130, 1098; δ_{H} (400 MHz, CDCl_3) 1.07 (3H, br s), 1.19 (3H, br s), 1.89 (1H, br s), 2.40 (4H, br s), 2.89-2.92 (4H, m), 3.21 (2H, br s), 3.50 (2H, br s), 4.41 (1H, s), 7.24-7.84 (11H, 3m); $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O} \cdot 0.9 \text{H}_2\text{O}$ requires:

25 C: 74.75 H: 7.91 N: 10.06 Found: C: 74.68 H: 7.56 N: 10.38.

Example 24**Preparation of (\pm) 4-((α -((4-Allyl)-1-piperazinyl))-2-naphthylmethyl)-N,N-diethylbenzamide (compound 38)**

- 5 The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3, but substituting compound 3 for compound 37.

ν_{\max} (KBr)/ cm^{-1} 3053, 2968, 2805, 1629, 1426, 1288, 1141, 1095, 921, 817; δ_{H} (400 MHz, CDCl_3) 1.06 (3H, br s), 1.19 (3H, br s), 2.49 (6H, br s), 3.00 (2H, m), 3.20 (2H, br
10 s), 3.49 (2H, br s), 4.41 (1H, s), 5.08-5.22 (2H, m), 5.78-5.92 (1H, m), 7.26-7.84 (11H, m); $\text{C}_{25}\text{H}_{34}\text{N}_3\text{OCl}_3 \cdot 0.6 \text{ H}_2\text{O}$ requires:
C: 76.99 H: 8.07 N: 9.29 Found: C: 77.06 H: 8.09 N: 9.32 %.

Scheme 8

The compounds according to Examples 25-26 were synthesized as shown in Scheme 8 above.

H.**I. Preparation of (±) 4-((α-Hydroxy)-4-xylyl)-N,N-diethylbenzamide (compound 39)**

- 5 The compound 39 was prepared by following the synthesis procedure as described for compound 31, but substituting 4-chlorophenylmagnesiumbromide for 4-toluylmagnesiumbromide.

ν_{\max} (KBr)/cm⁻¹ 3364, 2970, 1602, 1455, 1381, 1291, 1101, 1054, 802; δ_{H} (400 MHz, CDCl₃) 1.09 (3H, br s), 1.22 (3H, br s), 2.33 (3H, s), 2.55 (1H, br s), 3.24 (2H, br s), 3.52 (2H, br s), 5.78 (1H, d, J 3), 7.11-7.41 (8H, m);

II. Preparation of (±) 4-((α-Chloro)-4-xylyl)-N,N-diethylbenzamide (compound 40)

- 15 The compound 40 was prepared by following the synthesis procedure as described for compound 2.

Used for the next step without further purification.

20 **Example 25**

Preparation of (±) 4-((α-(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide (compound 41)

- The compound of this Example was prepared by following the synthesis procedure as described for compound 3.
- 25

m.p. 129-132°C (from acetonitrile), ν_{\max} (KBr)/cm⁻¹ 3320, 2957, 2811, 1610, 1437, 1285, 1128, 1010, 838; δ_{H} (400 MHz, CDCl₃) 1.10 (3H, br s), 1.20 (3H, br s), 1.83 (1H, br s), 2.30 (3H, s), 2.34 (4H, br s), 2.86-2.89 (4H, m), 3.24 (2H, br s), 3.51 (2H, br s), 4.20 (1H, s), 7.06-7.46 (8H, 3m); C₂₃H₃₁N₃O requires:
5 C: 75.58 H: 8.55 N: 11.50 Found: C: 75.30 H: 8.54 N: 11.56.

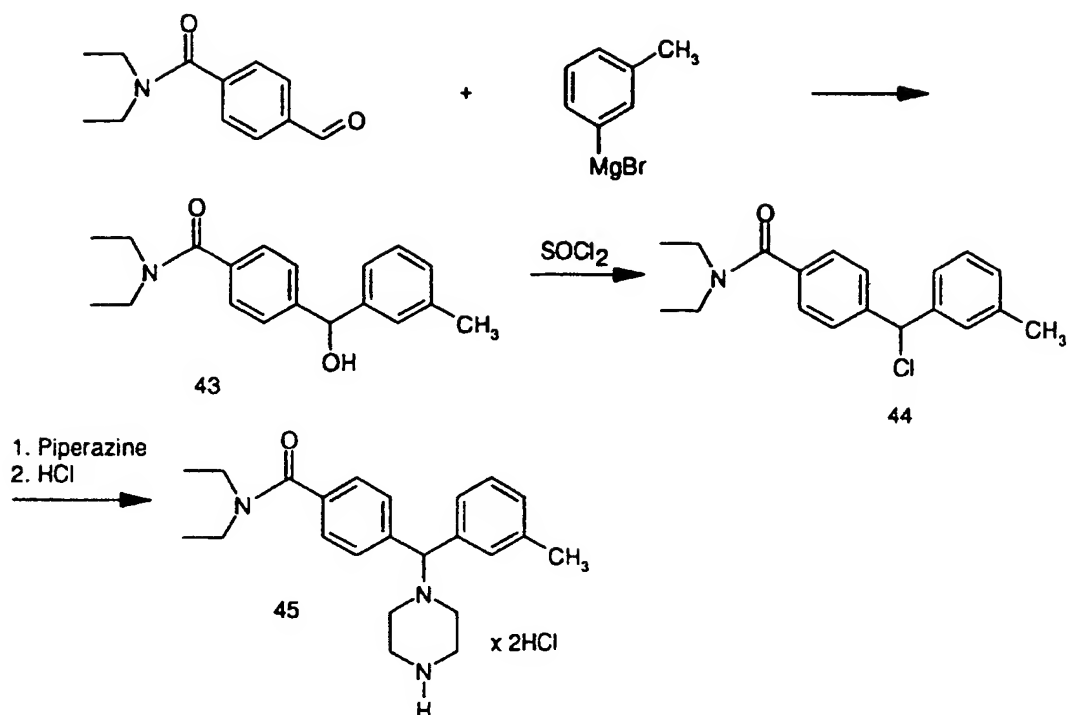
Example 26

Preparation of (±) 4-((α-((4-Allyl)-1-piperazinyl))-4-xylyl)-N,N-diethylbenzamide •

10 2HCl (compound 42)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

15 m.p. >160°C dec. (from ether); ν_{\max} (KBr)/cm⁻¹ 3437, 2973, 2402, 1625, 1433, 1289, 1097, 944, 809; δ_{H} (400 MHz, CDCl₃, free base) 1.10 (3H, br s), 1.20 (3H, br s), 2.29 (3H, s), 2.35-2.60 (6H, m), 3.03 (2H, m), 3.24 (2H, br s), 3.52 (2H, br s), 4.22 (1H, s), 5.12-5.23 (2H, m), 5.81-5.93 (1H, m), 7.05-7.45 (8H, 3m);

Scheme 9

5

The compounds according to Examples 27 were synthesized as shown in Scheme 9 above.

I

10 **I. Preparation of (\pm) 4-((α -Hydroxy)-3-xylyl)-N,N-diethylbenzamide (compound 43)**

The compound 43 was prepared by following the synthesis procedure as described for compound 31, but substituting 4-chlorophenylmagnesiumbromide for m-toluylmagnesiumbromide.

15

ν_{\max} (KBr)/ cm^{-1} 3406, 2972, 1613, 1429, 1360, 1287, 1097, 1053, 789; δ_{H} (400 MHz, CDCl_3) 1.10 (3H, br s), 1.22 (3H, br s), 2.34 (3H, s), 2.55 (1H, d, J 3.5), 3.25 (2H, br s), 3.52 (2H, br s), 5.80 (1H, d, J 3), 7.12-7.42 (8H, m);

5

II. Preparation of (\pm) 4-((α -Chloro)-3-xylyl)-N,N-diethylbenzamide (compound 44)

The compound 44 was prepared by following the synthesis procedure as described for compound 2.

10

Used for the next step without further purification.

Example 27

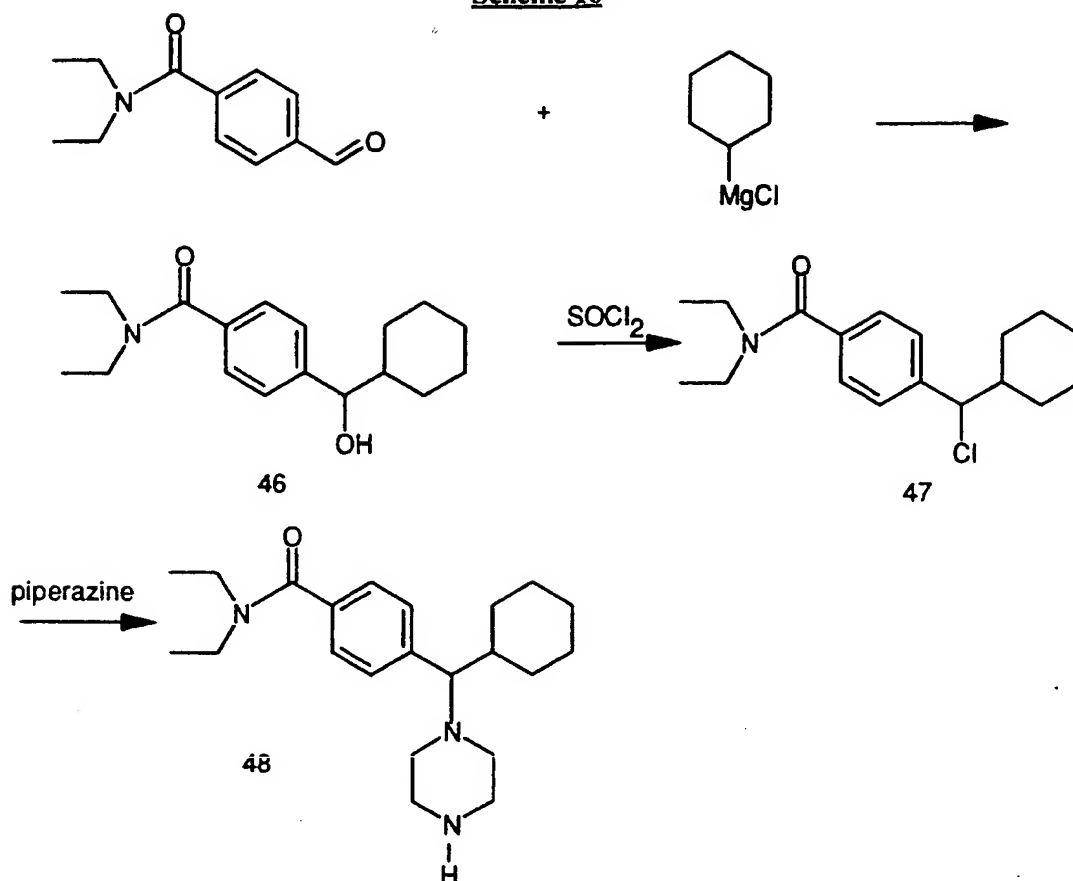
Preparation of (\pm) 4-((α -(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 45)

15

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

20 m.p. $>130^\circ\text{C}$ dec. (from ether), ν_{\max} (KBr)/ cm^{-1} 2971, 2805, 2715, 1624, 1434, 1289, 1096, 783; δ_{H} (400 MHz, CDCl_3 , free base) 1.10 (3H, br s), 1.20 (3H, br s), 2.31 (3H, s), 2.35-2.45 (5H, m), 2.89-2.92 (4H, m), 3.25 (2H, br s), 3.51 (2H, br s), 4.19 (1H, s), 6.98-7.46 (8H, 4m);

47

Scheme 10

5

The compounds according to Example 28 were synthesized as shown in Scheme 10 above.

I

I. Preparation of (\pm) 4-((α -Hydroxy)-cyclohexylmethyl)-*N,N*-diethylbenzamide (compound 46)

10

The compound 46 was prepared by following the synthesis procedure as described for compound 31.

δ_H (400 MHz, $CDCl_3$) 0.85-2.0 (18H, m), 3.26 (2H, br s), 3.53 (2H, br s), 4.35-4.43 (1H, m), 7.28-7.36 (4H, m);

5 **II. Preparation of (\pm) 4-((α -Chloro)-cyclohexylmethyl)-N,N-diethylbenzamide (compound 47)**

The compound 47 was prepared by following the synthesis procedure as described for compound 2.

10

Used for the next step without further purification.

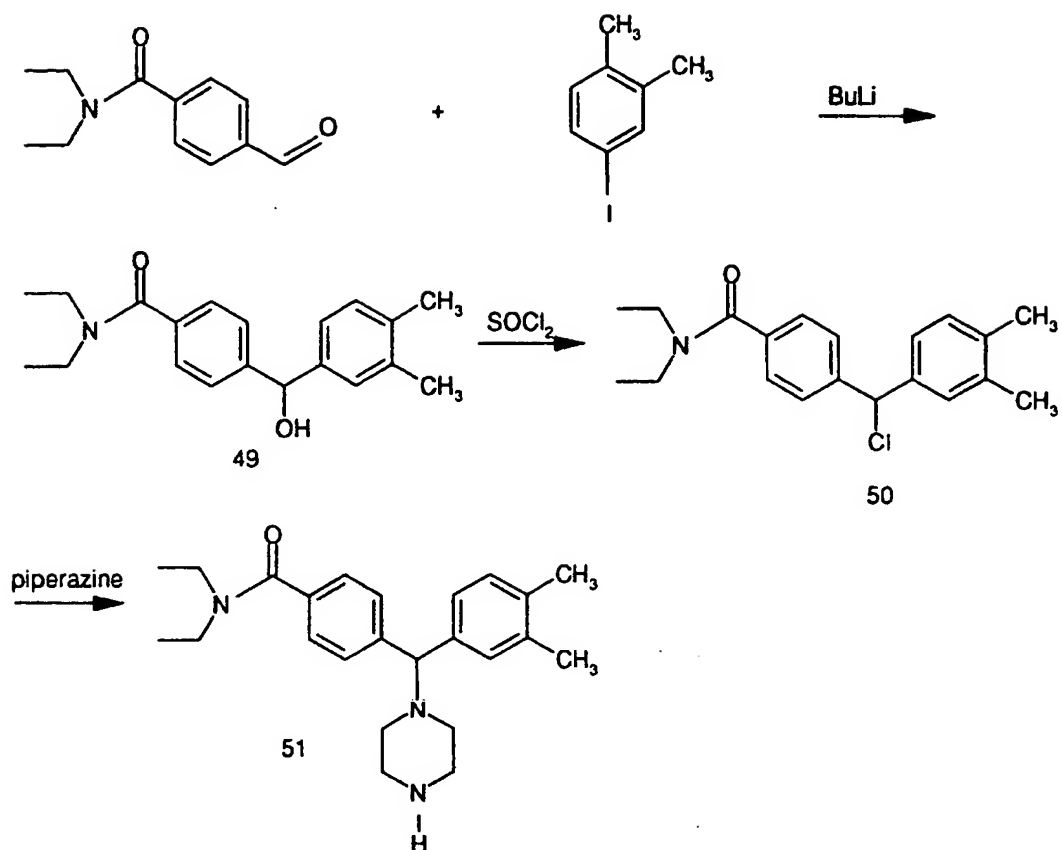
Example 28

Preparation of (\pm) 4-((α -(1-Piperazinyl))-cyclohexylmethyl)-N,N-diethylbenzamide (compound 48)

15

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

20 m.p. 113-116°C (from acetonitrile), ν_{max} (KBr)/ cm^{-1} 3330, 2936, 2845, 1623, 1431, 1286, 1096, 823; δ_H (400 MHz, $CDCl_3$) 0.64-2.02 (18H, m), 2.18-2.40 (4H, m), 2.75-2.87 (4H, m), 3.06 (1H, d, J 8.8), 3.27 (2H, br s), 3.52 (2H, br s), 7.11 (2H, d, J 8.4), 7.29 (2H, d, J 8.4);

Scheme 11

5

The compounds according to Examples 29 were synthesized as shown in Scheme 11 above.

K.**I. Preparation of (±) 4-((α-Hydroxy)-3,4-dimethylbenzyl)-N,N-diethylbenzamide**10 **(compound 49)**

The compound 49 was prepared by following the synthesis procedure as described for compound 1.

δ_{H} (400 MHz, CDCl_3) 1.09 (3H, br s), 2.23 (6H, s), 2.85 (1H, d, J 3), 3.24 (2H, br s), 3.51 (2H, br s), 5.73 (1H, d, J 2), 7.03-7.12 (m, 3H), 7.26-7.39 (m, 4H);

II. Preparation of (\pm) 4-((α -Chloro)-3,4-dimethylbenzyl)-N,N-diethylbenzamide
(compound 50)

The compound 50 was prepared by following the synthesis procedure as described for compound 2.

10 Used for the next step without further purification.

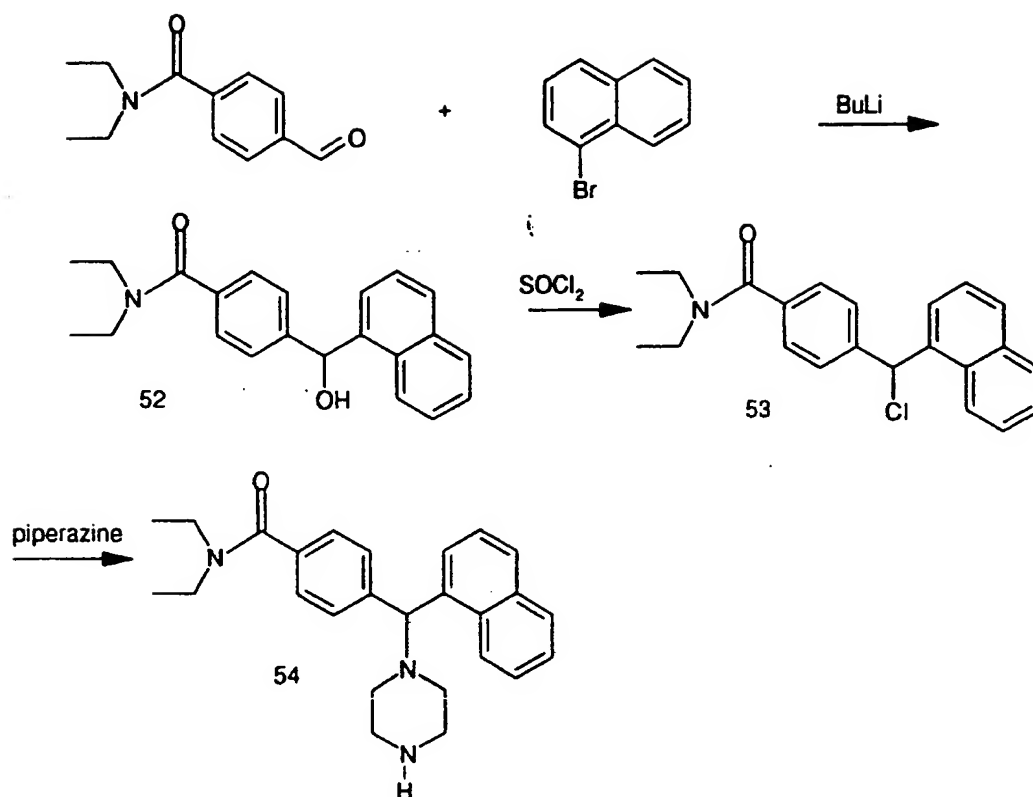
Example 29

Preparation of (\pm) 4-((α -(1-Piperazinyl))-3,4-dimethylbenzyl)-N,N-diethylbenzamide
(compound 51)

15

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

ν_{max} (KBr)/ cm^{-1} 3304, 2939, 2810, 1626, 1429, 1286, 1096, 846; δ_{H} (400 MHz, CDCl_3)
20 1.11 (3H, br s), 1.20 (3H, br s), 1.87 (1H, br s), 2.20 (3H, s), 2.22 (3H, s), 2.34 (4H, br s),
2.86-2.89 (4H, m), 3.25 (2H, br s), 3.51 (2H, br s), 4.15 (1H, s), 7.02-7.15 (3H, m), 7.26-
7.30 (2H, m), 7.42-7.46 (2H, m);

Scheme 12

5

The compounds according to Examples 30 were synthesized as shown in Scheme 12 above.

L

I Preparation of (±) 4-((α-Hydroxy)-1-naphthylmethyl)-N,N-diethylbenzamide
(compound 52)

10

The compound 52 was prepared by following the synthesis procedure as described for compound 1.

δ_{H} (400 MHz, CDCl_3) 1.06 (3H, br s), 1.20 (3H, br s), 3.01 (1H, d, J 4), 3.21 (2H, br s), 3.49 (2H, br s), 6.47 (1H, d, J 4), 7.24-7.48 (7H, m), 7.55-7.58 (1H, m), 7.78-7.87 (2H, m), 7.98-8.01 (1H, m);

5

II. Preparation of (\pm) 4-((α -Chloro)-1-naphtylmethyl)-N,N-diethylbenzamide (compound 53)

The compound 53 was prepared by following the synthesis procedure as described for
10 compound 2.

Used for the next step without further purification.

Example 30

15 **Preparation of (\pm) 4-((α -(1-Piperazinyl))-1-naphtylmethyl)-N,N-diethylbenzamide (compound 54)**

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

20

ν_{max} (KBr)/ cm^{-1} 3307, 3050, 2966, 2814, 1625, 1431, 1287, 1098, 843, 797; δ_{H} (400 MHz, CDCl_3) 1.04 (3H, br s), 1.17 (3H, br s), 2.14 (1H, br s), 2.40 (2H, br s), 2.46 (2H, br s), 2.83-2.95 (4H, m), 3.17 (2H, br s), 3.48 (2H, br s), 5.05 (1H, s), 7.22-7.28 (2H, m), 7.40-7.54 (5H, m), 7.70-7.94 (3H, m), 8.40-8.43 (1H, m);

25

Piperazine ring modifications: General Experimental and Examples

The compounds according to Examples 31-42 were synthesized as shown in Scheme 13 below.

M.**I. Preparation of 2-Dimethyl-5-methyl-piperazine-3,5-dione (compound 55)**

N-*t*-Butoxycarbonyl-2-aminoisobutyric acid (5.0g, 25mmol) and D,L-alanine methyl ester hydrochloride (3.5g, 25mmol) was dissolved in dry dichloromethane (50mL) and cooled to 0°C. Triethylamine (3.5mL, 25mmol) and then 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (4.8g, 25mmol) was added and the mixture was stirred at 0°C until lumps dissolved. The reaction mixture was then left in the freezer 4d at -20°C. The organic solution was washed with water, 1M citric acid (aq.), water, dried (Na₂SO₄) and evaporated *in vacuo* to give 6.0g (83%) of coupling product. Most of the coupling product (5g) was dissolved in formic acid (50mL) and stirred 12h at 25°C. The acid was removed *in vacuo* and the residue dissolved in 2-butanol and heated at reflux for 4h. The solution was cooled to 0°C and the crystals filtered off and dried *in vacuo* at 100°C. Yield 2.6g of pure compound 55 (82%) which could be recrystallized from methanol, mp: >300°C. IR (KBr) (cm⁻¹): 3000 (br), 1680 (s) (C=O). ¹H NMR (D₂O): δ = 4.75 (s, 2H, NH), 4.21 (q, 1H, CHMe), 1.50-1.42 (m, 9H, 3Me). C₇H₁₂N₂O₂ requires C: 53.83, H: 7.74, N: 17.94. Found C: 53.89, H: 7.90, N: 17.79.

II. Preparation of 2-Dimethyl-5-methyl-piperazine dihydrochloride (compound 56)

Compound 55 (2.2g, 14mmol) was dissolved on dry THF (120mL). Lithium aluminum hydride (42mL, 1M in THF) was added in small portions. When addition complete, the solution was heated at reflux over night. The solution was allowed to cool, then excess hydride was destroyed by dropwise addition of water (1.6mL), NaOH (1.6mL, 15% solution) and water (4.8mL). The granular precipitate was filtered off and solvent evaporated *in vacuo*. The residue was dissolved in dichloromethane, dried (K₂CO₃) and

evaporation of solvent in vacuo gave 1.5g (84%). Treatment with excess HCl in ether gave the dihydrochloride compound 56 which could be recrystallized from methanol/ether mp: >300°C. IR (cm⁻¹), KBr: 2760, 1570 (R₂NH₂⁺). MS (amine): 128, 113, 84, 71, 58. ¹H NMR (D₂O+DSS): δ = 2.70-2.50 (m, 5H, CH₂-N, CH-N), 1.14 (s, 3H, 1 Me), 1.00-0.94 (s+d, 6H, 2 Me). C₇H₁₆N₂·2HCl requires C: 41.80, H: 9.02, N: 13.93. Found C: 42.03, H: 9.24, N: 14.00.

Example 31

Preparation of 4-(4-(2-Dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 57)

4-(Chloro-(3-methoxyphenyl)methyl)-N,N-diethylbenzamide (0.61g, 2.0mmol) and compound 56 (0.50g, 3.9mmol) was dissolved in dry acetonitrile (5mL). Potassium carbonate (0.26g, 2.0mmol) was added and the mixture heated at reflux for 2d. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica (CH₂Cl₂/MeOH/NH₃(aq.)), 98:1:1 to 95:5:1 to yield 0.65g (79%). Treatment with excess of HCl in ether, filtering and drying crystals *in vacuo* over KOH gave the dihydrochloride compound 57, mp: 134-36°C. IR (HCl salt, KBr) (cm⁻¹): 3400 (br, OH), 2900 (br, R₂NH₂⁺), 1600 (s, C=O or R₂NH₂⁺), 1283, 1038 (C-O). MS (amine) 3 peaks: 423, 353, 325, 296, 127. ¹H NMR: (amine, CDCl₃): δ = 7.40-6.60 (m, 8H, Ar-H), 5.26, 5.25, 4.61 (3s, 1H, CHAr₂), 3.70 (s, 3H, MeO), 3.4, 3.2 (2 br. s, 4H, MeCH₂), 3.1-2.0 (m, 5H, piperazine-H), 1.3-0.9 (m, 15H, 5Me). C₂₆H₃₇N₃O₂·2HCl requires C: 62.89, H: 7.92, N: 8.46. Found C: 63.41, H: 8.38, N: 8.56.

Example 32

Preparation of 4-(4-(1-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 58)

Compound 57 (0.39g, 0.92mmol) was dissolved in dry acetonitrile (5mL). Potassium carbonate (0.13g, 0.92mmol) and allyl bromide (90μL, 1.02mmol) was added. After 3h at

25°C the solvent was evaporated and the residue purified by flash chromatography on silica (CH₂Cl₂/MeOH), 98:2 to 95:5 to give a total of 0.39g (92%). Treatment with excess of HCl in ether, filtering and drying crystals in vacuo over KOH gave the dihydrochloride, compound 58, mp: 105-21°C. IR (HCl salt, KBr) (cm⁻¹): 3400 (br, OH), 2500 (br, R₂NH₂⁺), 16200 (s) (C=O or R₂NH₂⁺), 1285, 1043 (C-O). ¹H NMR: (amine, CDCl₃): δ = 7.50-6.60 (m, 8H, Ar-H), 5.70 (m, 1H, allyl-H), 5.00 (m, 2H, allyl-H), 4.70 (s, 1H, CHAr₂), 3.70 (s, 3H, MeO), 3.5 + 3.3 (2 br. s, 4H, MeCH₂), 3.0-1.9 (m, 7H, piperazine-H), 1.2-0.8 (m, 15H, 5Me). C₂₉H₄₁N₃O₂ x2HCl requires C: 64.91, H: 8.08, N: 7.83. Found C: 65.70, H: 8.60, N: 8.29.

10

N.**I. Preparation of 4-Allyl-2-dimethyl-5-methyl-piperazine (compound 59)**

15 **Compound 56** (0.14g, 0.91mmol) was dissolved in acetonitrile and allyl bromide (80μL, 0.91mmol) was added at 0°C. After 1h another portion of allyl bromide was added. After 2h the solvent was evaporated and the residue purified by flash chromatography on silica (CH₂Cl₂/MeOH), 95:5 to 80:20 to give the monoallyl compound 59, 116mg (69%).

Example 33**Preparation of 4-(1-(4-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 60)**

The compound of this Example was prepared by following the synthesis procedure as described for Example 3.

25

Mp: 125-30°C. IR (2HCl, KBr) (cm⁻¹): 3430(br), 2978, 2480(br.), 1607, 1436, 1285. MS(free amine): 366, 296, 167. ¹H NMR: (D₂O + DSS): δ = 7.60-6.90 (m, 9H, Ar-H), 6.0-5.5 (m, 4H, allyl-H + Ar₂CH), 3.80 (2s, 3H, MeO), 4.0-3.7 (m, 11H, allyl-H, piperazine-H,

amide-CH₂), 1.3-1.0 (m, 15H, piperazine-Me, amide-Me). Anal. calc. for C₂₉H₄₁N₃O₂ x 2HCl x 2.9 H₂O: C:59.15, H:8.35, N:7.14. Found: C: 59.05, H:8.00, N: 7.22.

Example 34

5 **Preparation of 4-(1-(2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 61)**

56 (42mg, 0.33mmol) and potassium carbonate (46mg, 0.33mmol) was dissolved in water (2mL) and di-*t*-butyl dicarbonate (79mg, 0.36mmol) was added. After stirring 1h the
10 solvent was evaporated *in vacuo* and the residue purified by chromatography on silica (CH₂Cl₂/MeOH), 90:10 to give 43 mg of the mono-N-Boc protected 55 which was dissolved in dry acetonitrile together with potassium carbonate (26mg, 0.19mmol) and 4-(Chloro-(3-methoxyphenyl)methyl)-N,N-diethylbenzamide (63mg, 0.19mmol). After heating 4 days at reflux, the solvent was removed *in vacuo* and residue purified by
15 chromatography on silica (CH₂Cl₂/MeOH), 100:0, 95:5. Treatment with formic acid (5mL) for 3h, evaporation of solvent *in vacuo* and extraction of the residue with CH₂Cl₂/1M NaOH, drying of the organic phase (K₂CO₃) and evaporation of solvent *in vacuo* gave 27mg (33%) of the free amine. Treatment with excess HCl in ether gave the dihydrochloride which was dissolved in water and freeze-dried., mp: 145-50°C. IR (2HCl, KBr) (cm⁻¹):
20 3500-3400(br), 1601, 1442, 1285. MS(free amine): 423, 296, 325, 127. ¹H NMR: (CDCl₃): δ = 7.4-6.6 (m, 8H, Ar-H), 5.39, 5.36 (2s, 1H, Ar₂CH), 3.75 (s, 3H, MeO), 3.5, 3.25 (2 br. s, 4H, amide-Me), 2.80, 2.50, 2.05 (3m, 5H, piperazine-H), 1.5 (br.s, 1H, N-H), 1.25-1.0 (br. m, 6 H, amide-Me), 1.15 (s, 3H, Me), 0.90 (d, 3H, Me), 0.85 (s, 3H, Me). Calc. for C₂₆H₃₇N₃O₂ x 2HCl x 7.4 H₂O: C:49.58, H:8.61, N:6.67. Found: C: 49.61, H:7.73, N:
25 6.56.

Q.**I. Preparation of 4-(Phenyl-hydroxymethyl)-N,N-diethylbenzamide (compound 62)**

The compound 62 was prepared by following the synthesis procedure as described for
5 compound 1.

MS: 282, 211, 165, 105. ¹H NMR: (CDCl₃): δ = 7.38-7.20 (m, 9H), 5.80 (d, J=3.5Hz, 1
H), 3.5, 3.2 (2br.s, 4H), 1.2, 1.05 (2br. s, 6H).

10 **II. Preparation of 4-(Chloro-phenyl-methyl)-N,N-diethylbenzamide (compound 63)**

The compound 63 was prepared by following the synthesis procedure as described for
compound 2.

15 GC-MS (2 peaks): 296, 225, 165, 121. and 300, 266, 229, 195, 165. ¹H NMR: (CDCl₃): δ
= 7.45-7.20 (m, 9H), 6.09 (s, 1H), 3.4 (br. m, 4H), 1.1 (br. m, 6H).

Example 35

20 **Preparation of 4-((1-piperazinyl)-benzyl)- N,N-diethylbenzamide dihydrochloride
(compound 64)**

The compound of this Example was prepared by following the synthesis procedure as
described for compound 3.

Mp: 157-69°C. IR (amine, CDCl₃ in KBr cell) (cm⁻¹): 3690, 3630, 1613, 1435, 1265. MS (free amine): 351, 306, 295, 266, 194, 165. ¹H NMR: (free amine, CDCl₃): δ = 7.46-7.16 (m, 9H, Ar-H), 4.24 (s, 1H, CHAr₂), 3.5 + 3.2 (2 br. s, 4H, MeCH₂), 2.89 (m, 4H, piperazine-H), 2.36 (br. s, 4H, piperazine-H), 1.94 (br s, 1H, NH), 1.2 + 1.1 (2 br. s, 6H, 2Me). Anal. calc. for C₂₂H₂₉N₃O x 2HCl x 1.90 H₂O, C: 57.61, H: 7.65, N: 9.16. Found C: 57.59, H: 7.66, N: 8.92.

Example 36

10 Preparation of 4-((4-Allyl-1-piperazinyl)-benzyl)-N,N-diethylbenzamide dihydrochloride (compound 65)

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

15 Mp: 175-205°C. IR (amine, CDCl₃ in KBr cell) (cm⁻¹): 3689, 1613, 1455, 1434, 1290, 1143. MS (free amine): 391, 165, 125. ¹H NMR: (free amine, CDCl₃): δ = 7.42-7.12 (m, 9H, Ar-H), 5.81 (m, 1H, allyl-H), 5.10 (m, 2H, allyl-H), 4.23 (s, 1H, CHAr₂), 3.5 + 3.2 (2 br. s, 4H, MeCH₂), 3.00 (m, 2H, allyl-H), 2.6-2.4 (br. s, 8H, piperazine-H), 1.1 (2 br. s, 20 6H, 2Me). Anal. calc. for C₂₅H₃₅N₃O x 2HCl x 1.0 H₂O, C: 62.23, H: 7.73, N: 8.71. Found C: 62.22, H: 7.49, N: 8.42.

E

I. Preparation of 2-Hydroxymethyl-5-methyl-piperazine-3,5-dione (compound 66)

25

(D,L)-N-*t*-Butoxycarbonyl-alanine (5.0g, 26mmol) was dissolved in methylene chloride (50mL) with triethyl amine (8.1mL), dried with 4A molecular sieves and transferred to dry flask under nitrogen. *i*-Butyl chloroformate (3.8mL, 29mmol) was added at -10°C. The Solution was stirred 15min, then D,L-serine methylester hydrochloride (4.1g, 26mmol) was 30 added and the solution was allowed to reach 25°C and stirred 12h. Washing the solution

with brine, drying (MgSO₄) and evaporating solvent *in vacuo* gave a solid which was treated with formic acid for 1h. The acid was removed *in vacuo* and the residue dissolved in anhydrous 2-butanol (5mL) and heated at reflux 2 days. The solvent was removed and the residue crystallized when treated with acetone to give 1g of compound 66 (24%).

5

II. Preparation of 2-Hydroxymethyl-5-methyl-piperazine (compound 67)

The compound 67 was prepared by following the synthesis procedure as described for
10 compound 55.

II. Preparation of 2-(*t*-Butyldiphenylsilyloxy)methyl-5-methyl-piperazine (compound 68)

15 Compound 67 (0.41g, 3.1mmol) was dissolved in dry DMF (5mL). Chloro-*t*-butyldiphenylsilane (0.95g, 3.4mmol) and imidazole (0.47g, 6.9mmol) was added and stirring was continued 12h. The product was extracted by adding ethyl acetate, brine and 1M NaOH and shaking. The organic phase was dried and evaporated *in vacuo*. Chromatography of the residue on silica (CH₂Cl₂/MeOH, 100:0, 95:5, 90:10 and 80:20)
20 gave 0.39g (34%) pure compound 68.

Example 37

Preparation of 4-(4-(2-Hydroxymethyl-5-methyl)piperazinyl-benzyl)-N,N-diethyl-benzamide dihydrochloride (compound 69)

25

The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp: 145-50°C. IR (2HCl, KBr) (cm⁻¹): 3300(br), 2700(br), 1612, 1446, 1382, 1296, 1080.
30 MS(free amine): 381, 218, 181, 91. ¹H NMR: (free amine, CDCl₃): δ = 7.44-7.18 (m, 9H,

Ar-H), 5.17, 5.14 (2s, 1H, ArCH₂), 3.75-2.60 (m, 12H, piperazine-H, amide-CH₂), 2.02 (m, 1H, piperazine-H), 1.30-1.05 (m, 9H, piperazine-Me + amide-Me). Anal. calc. for C₂₄H₃₃N₃O₂ x 2HCl x 1.8 H₂O: C: 57.55, H: 7.77, N: 8.39. Found: C: 57.05, H: 7.67, N: 8.19.

5

Example 38

Preparation of 4-((4-(2-Hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 70)

10 The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp: 185-90°C. IR (2HCl, KBr) (cm⁻¹): 3500-2500(br), 1596, 1440, 1045. ¹H NMR: (free amine, CDCl₃): δ = 7.40-6.60 (m, 8H, Ar-H), 5.05, 5.10 (2s, 1H, Ar₂CH), 3.70 (s, 3H, MeO), 3.8-2.5 (m, 12H, piperazine, amide CH₂) 1.2-1.0 (br. s, 9H, amide-Me, piperazine-Me).

15

Example 39

Preparation of 4-((4-(1-Allyl-2-hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 71)

20

The compound of this Example was prepared by following the synthesis procedure as described for Examples 2 and 3.

25 Mp: 125-30°C. IR (2HCl, KBr) (cm⁻¹): 3400(br), 1603, 1445, 1285. MS(free amine): two peaks: 310, 239, 135 and 312, 241, 135. ¹H NMR: (free amine, CDCl₃): δ = 7.50-6.70 (m, 8H, Ar-H), 5.80, 5.20, 5.00 (3m, 3H, allyl-H), 4.0-2.3 (m, 14H, piperazine-H, allyl-H, amide-CH₂) 3.80 (s, 3H, MeO), 1.2 (br. s, 6H, amide-Me). Anal. calc. for C₂₅H₃₅N₃O₃ x 2HCl x 3.7 H₂O: C: 55.57, H: 8.06, N: 6.94. Found: C: 55.53, H: 7.82, N: 7.16.

30

Ω**I. Preparation of Methyl 3-(hydroxy-(2-naphtyl)methyl)phenyl ether (compound 72)**

- 5 The compound 72 was prepared by following the synthesis procedure as described for compound 1.

MS: 264, 155, 135, 128, 109, 101. ¹H NMR: (CDCl₃): δ = 7.90-6.78 (m, 11H, Ar-H), 5.98 (d, *J* = 3.5Hz, 1H, Ar₂H), 3.78 (s, 3H, MeO), 2.32 (d, *J* = 3.5Hz, 1H, OH).

10

II. Preparation of Methyl 3-(chloro-(2-naphtyl)methyl)phenyl ether (compound 73)

The compound 73 was prepared by following the synthesis procedure as described for compound 2.

15

GC-MS (2 peaks): 278, 247, 215, 171, 155, 135 and 282, 248, 247, 231, 215. ¹H NMR: (CDCl₃): δ = 7.86-6.81 (m, 11H, Ar-H), 6.25 (s, 1H, Ar₂H), 3.76 (s, 3H, MeO).

III. Preparation of 4-Allyl-2-methylpiperazine (compound 74)

20

2-Methylpiperazine (0.4g, 4mmol) was dissolved in acetonitrile (5mL) and allyl bromide (86μL, 1mmol) was added at 0°C. Stirring was continued at 0°C for 1h, then at 25°C for 6h. Evaporation of solvent *in vacuo* and chromatography on silica (CH₂Cl₂/MeOH, 80:20) gave 80mg (57%) pure compound 74.

25

Example 40Preparation of Methyl 3-((2-naphthyl)-(3-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 75)

- 5 The compound of this Example was prepared by following the synthesis procedure as described for compound 3.

Mp: 170-74°C. IR (KBr) (cm⁻¹): 3461, 2458, 1600, 1439, 1263, 1043. MS (amine): 386, 247, 215, 139, 112. ¹H NMR: (amine, CDCl₃): δ = 7.84-6.66 (m, 11H, Ar-H), 4.33 (s, 1H, CHAr₂), 3.74, 3.73 (2s, 3H, MeO), 3.00-2.70 (m, 6H, piperazine-H). 1.95, 1.65 (2m, 2H, piperazine-H), 0.98-0.92 (2d, J = 6.4 Hz, 3H, piperazine-Me). Anal. calc. for C₂₃H₂₆N₂O x2HCl x1.8 H₂O, C: 61.14, H: 7.05, N: 6.20. Found, C: 61.05, H: 6.48, N: 6.07.

10

Example 41

- 15 Preparation of Methyl 3-((2-naphthyl)-(4-allyl-2-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 76)

The compound of this Example was prepared by following the synthesis procedure as described for Example 3.

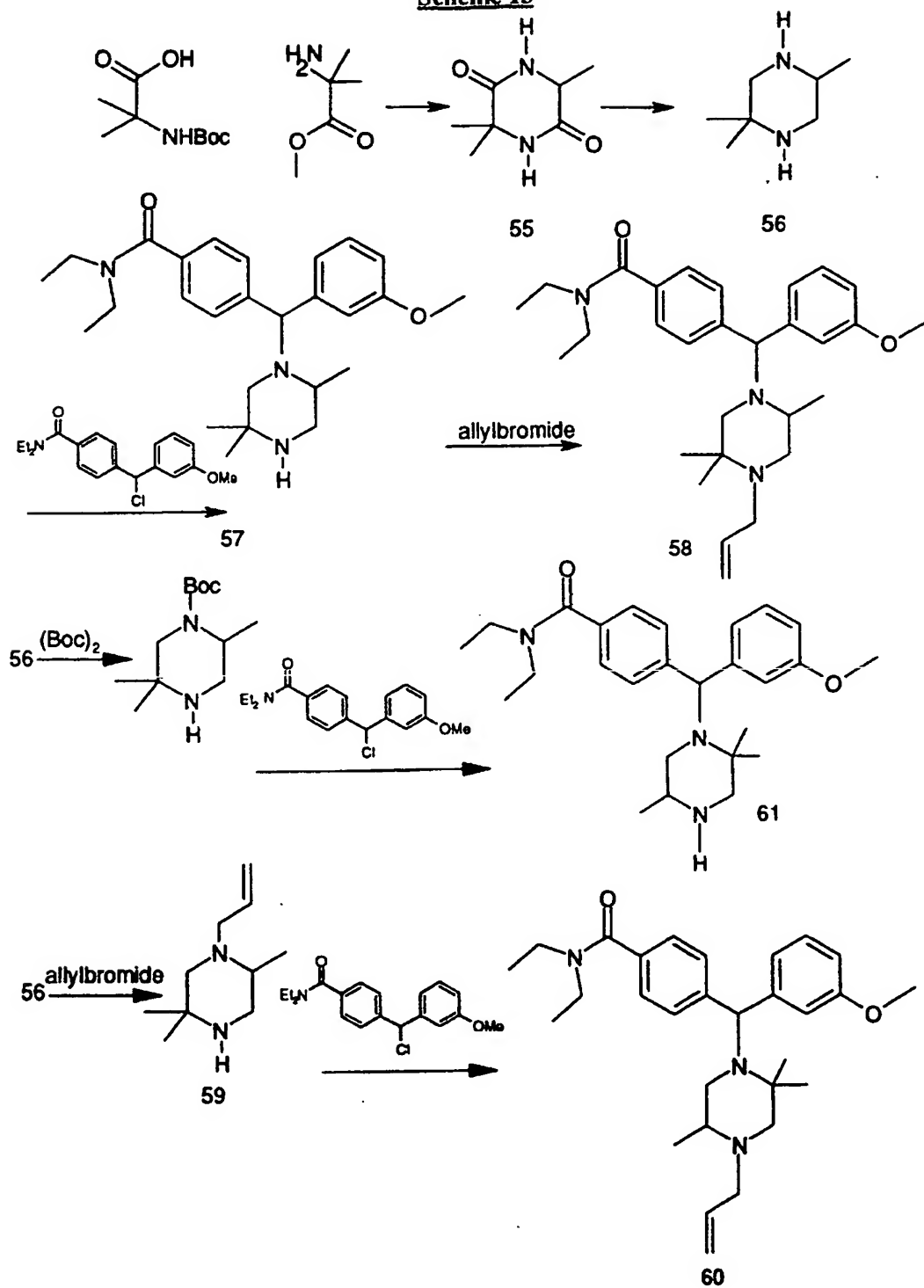
20

- Mp: 173-82°C. IR (KBr) (cm⁻¹): 3430, 2500, 2355, 1601, 1436, 1265, 1047. MS (amine): 386, 274, 247, 215, 139, 125. ¹H NMR: (amine, CDCl₃): δ = 7.86-6.66 (m, 11H, Ar-H), 5.82 (m, 1H, allyl-H), 5.12 (m, 2H, allyl-H), 4.95 (br. s, 1H, CHAr₂), 3.76, 3.75 (2s, 3H, MeO), 3.04-2.32 (m, 9H, piperazine-H), 1.15-1.11 (2d, 3H, Me). Anal. calc. for C₂₆H₃₂N₂O x2HCl x0.4 H₂O, C: 66.92, H: 7.08, N: 6.00. Found C: 67.03, H: 7.09, N: 5.88.
- 25

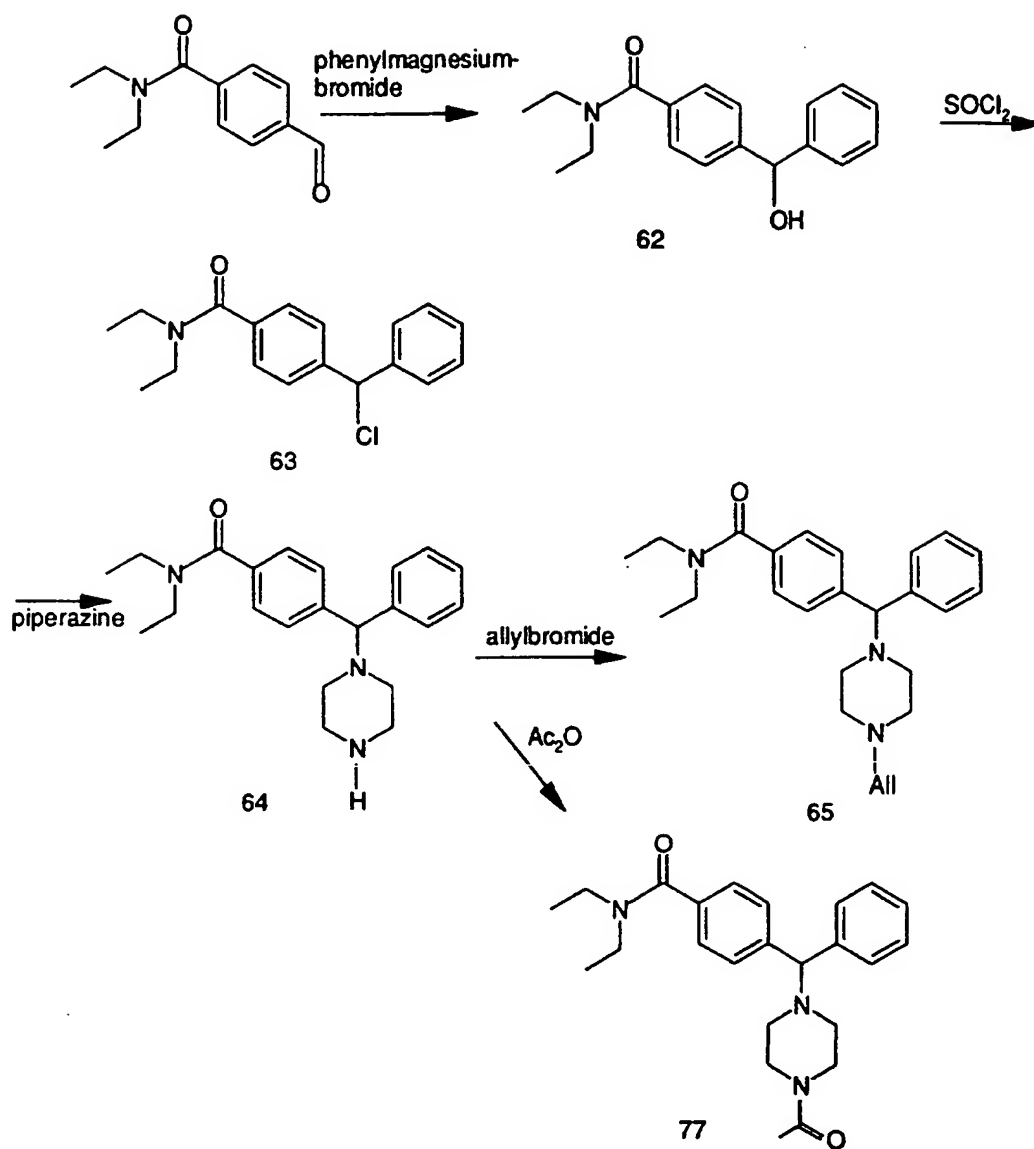
Example 42Preparation of 4-((4-Acetyl-1-piperazinyl)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77)

- 5 The free amine of **compound 64** (100 mg, 0.28 mmol) was dissolved in methylene chloride (5 ml), cooled to 0°C. Triethyl amine (43 µl, 0.31 mmol) was added and then acetyl chloride (22 µl, 0.31 mmol) was added dropwise. After 10 min, the solution was washed with potassium carbonate (10 %), dried (K₂CO₃) and evaporated *in vacuo*. The residue was purified by chromatography on silica (CH₂Cl₂/MeOH/NH₃, 95:5:0.5) to give 116 mg of
- 10 **compound 77** (~ 100 %).

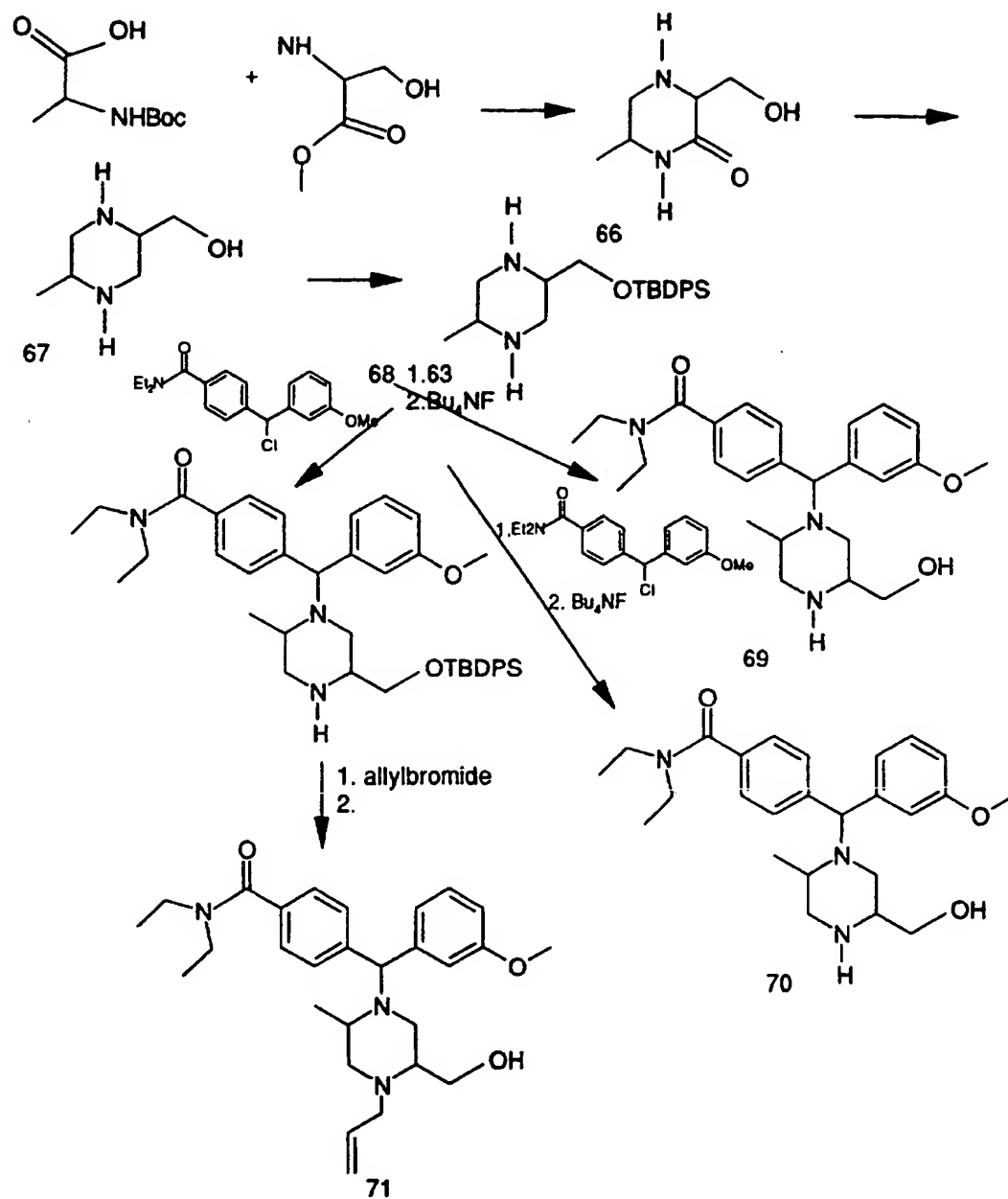
- Mp: 140-50°C. IR (KBr) (cm⁻¹): 3480(br), 2987, 2500(br), 1623, 1429, 1285, 1245. MS (free amine): 393, 267, 165, 127. ¹H NMR: (free amine, CDCl₃): δ = 7.46-7.18 (m, 9H, Ar-H), 4.25 (s, 1H, CHAr₂), 3.70- 3.15 (m, 8H, amide-CH₂, piperazine-H), 2.36 (m, 4H, piperazine-H), 2.05 (s, 3H, MeCO), 1.15 (br. m, 6H, amide-Me). Anal. calc. for C₂₄H₃₁N₃O₂ x 1HCl x 0.80 H₂O, C: 64.87, H: 7.62, N: 9.46. Found C: 65.01, H: 7.76, N: 9.42.
- 15

Scheme 13

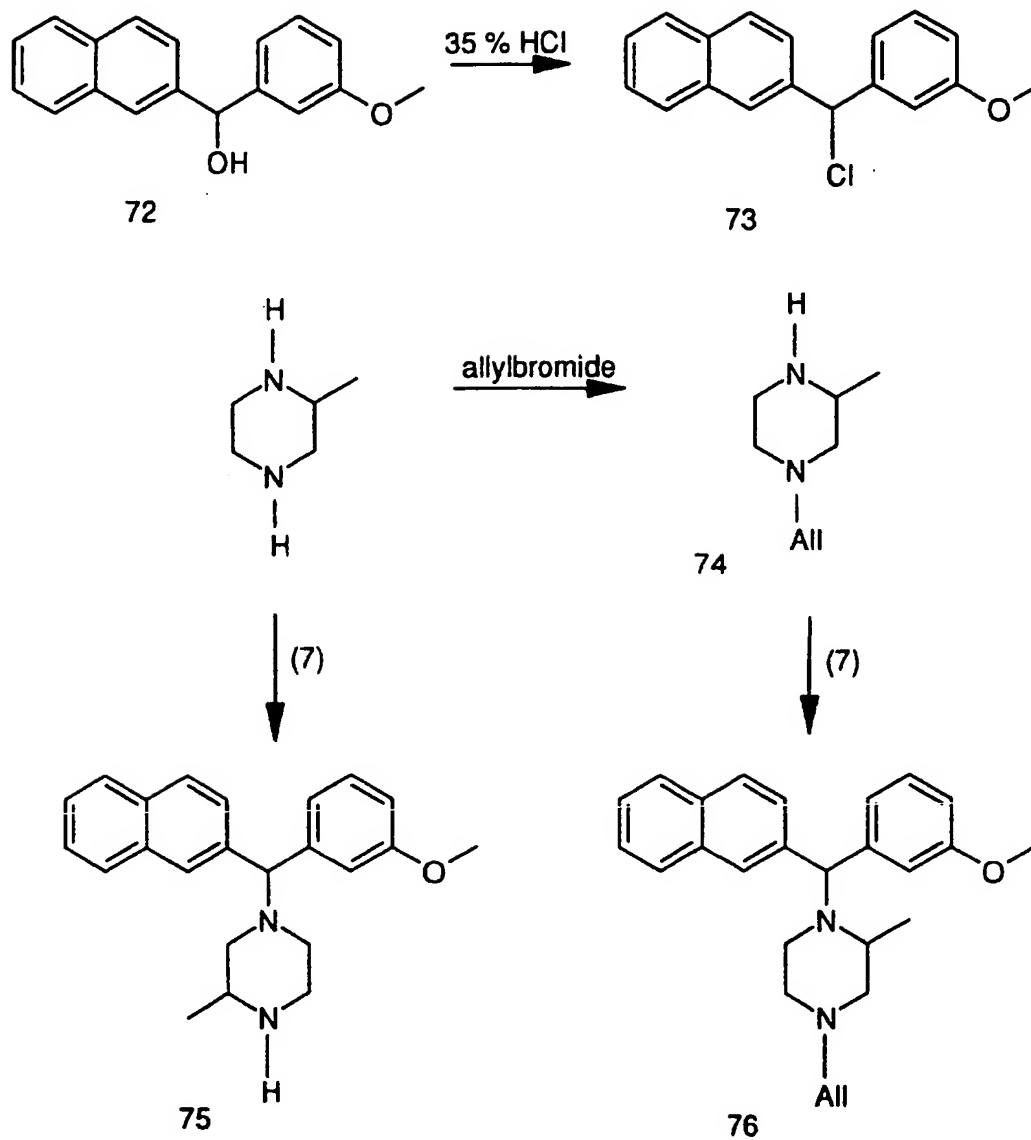
65



66



67



5

Diethylbenzamide replacements etc.

The compounds according to Examples 43-48 were prepared as shown in Scheme 14 below.

R.**I. Preparation of 4-((4-*t*-Butoxycarbonyl-1-piperazinyl)-benzyl)-benzoic acid (compound 78)**

- 5 **Compound 64** (6.0g, 17mmol) was dissolved in 6N hydrochloric acid and heated at 120°C for 3 days. The solution was then neutralized with aqueous NaOH (~12g). The solution was concentrated to 100mL, mixed with THF (100mL) and di-*t*-butyl dicarbonate (3.7g, 17mmol) added dissolved in THF (50mL). After stirring 1h at 25°C, the aqueous phase was acidified with 1M citric acid and extracted two times with ethyl acetate. The organic phase
10 was dried (K₂CO₃) and evaporated, and the residue purified by chromatography on silica (EtOAc/ heptane/ AcOH, 10:90:0 to 66:33:1) to give a total of 3.85g (57%) of **compound 78**.

Example 43

- 15 **Preparation of 4-((1-piperazinyl)-benzyl)-benzoic acid dihydrochloride (compound 79)**

- Compound 78** (150mg, 0.38mmol) was treated with excess HCl in acetic acid 1h. Acid removed *in vacuo* and residue dissolved in methanol and precipitated by addition of ether.
20 The precipitate was dried in vacuum at 100°C. Mp: 172-80°C. IR (KBr) (cm⁻¹): 3000(br), 1700, 1606, 1454. ¹H NMR: (DMSO-d₆): δ = 12.85 (s, 1H, CO₂H), 8.95 (s, 2H, NH), 7.92 -7.20 (m, 9H, Ar-H), 4.56 (s, 1H, Ar₂CH), 3.33 (s, 8H, piperazine-H). Anal. calc. for C₁₈H₂₀N₂O₂·2HCl, C:58.54, H:6.00, N:7.59. Found: C:59.9, H:6.47, N:7.88.

Example 44 and 45Preparation of Methyl 4-((4-*t*-butoxycarbonyl-1-piperazinyl)-benzyl)benzoate (compound 80) and Methyl 4-((1-piperazinyl)-benzyl)benzoate dihydrochloride (compound 81)

5
Compound 78 (0.15g, 0.38mmol) and cesium carbonate (0.25g, 0.76mmol) was mixed in DMF (2mL) and methyl iodide (72μL, 1.1mmol) was added. After 2h at 25°C, potassium carbonate (10% ,aq.) and the solution was extracted with ethyl acetate. After evaporation of solvent *in vacuo*, the residue was purified by chromatography on silica (EtOAc/ heptane,
10 30:70) to yield 0.13g (87%) of the methyl ester, compound 80. Boc-deprotection was achieved by treatment with excess HCl in methanol at 50°C. The solvent was removed and the residue was purified again on silica. The dihydrochloride, compound 81 (35mg), was prepared according to previous methodology. Mp: 185-95°C. IR (KBr) (cm⁻¹): 3400(br), 2700(br), 1720, 1612, 1430, 1285, 1190, 1112. MS (EI, free amine): 310, 265, 225, 206,
15 165. ¹H NMR: (D₂O/CD₃OD + DSS): δ = 8.20-7.34 (m, 9H, Ar-H), 5.03 (s, 1H, CHAr₂), 3.89 (s, 3H, MeO), 3.42 (m, 4H, piperazine-H), 3.08 (m, 4H, piperazine-H). Anal. calc. for C₁₉H₂₂N₂O₂ x 2HCl x 1H₂O, C:56.86, H:6.53, N:6.98. Found C:56.82, H:6.54, N:7.00.

S.**I. Preparation of 4-((1-piperazinyl)-benzyl)-benzamide dihydrochloride (compound 82)**

5

Compound 78 (0.11 g, 0.28mmol) was dissolved in dry methylene chloride/ THF, 1:1 (5mL) and cooled to -20°C. Triethylamine (78µL, 0.56mmol) was added and then i-butyl chloroformate (37µL, 0.28mmol). After 10 min, ammonia in methylene chloride (0.51mL, 1.1M, 0.56mmol) was added and the temperature was allowed to rise slowly to 25°C. After 10 3h, the solvent was removed *in vacuo* and the residue was purified by chromatography on silica (CH₂Cl₂/ MeOH/ NH₃, 95:5:1 and 90:10:1) to give 70mg (62%). Treatment with HCl in methanol 3h at 50°C, removal of solvent *in vacuo* and chromatography on silica (CH₂Cl₂/ MeOH/ NH₃, 90:10:1 and 80:20:1) gave the free amine which was converted to the dihydrochloride salt 82. Mp: 192-200°C. IR (KBr) (cm⁻¹): 3939(br), 3184(br), 15 2700(br), 1665, 1610, 1565, 1426. MS (amine): 295, 250, 210, 165, 152. ¹H NMR: (amine, CD₃OD): δ = 7.96 -7.22 (m, 9H, Ar-H), 4.93 (s, 2H, NH), 4.40 (s, 1H, Ar₂CH), 2.94 + 2.46 (2m, 8H, piperazine-H). Anal. calc. for C₁₈H₂₁N₃O x2HCl x1.1H₂O, C:55.70, H:6.54, N:10.83. Found C:55.83, H:6.76, N:10.75.

20 **Example 46****Preparation of 4-((1-piperazinyl)-benzyl)-N-ethylbenzamide hydrochloride (compound 83)**

The compound of this Example was prepared by following the synthesis procedure as 25 described for compound 82, but substituting ammonia for ethylamine.

Mp: 180-85°C. IR (KBr) (cm⁻¹): 3331(br), 2700(br), 1640, 1545, 1440, 1308. MS: (EI, amine) 323, 278, 267, 238, 195, 165. ¹H NMR: (amine, CD₃OD): δ = 7.84 -7.14 (m, 9H, Ar-H), 4.9 (br. s, NH), 4.45 (s, 1H, Ar₂CH), 3.40 (m, 2H, ethyl-CH₂), 3.25, 2.65 (2m, 8H, 30 piperazine-H), 1.20 (m, 3H, ethyl-Me).

Example 47**Preparation of 4-(1-piperazinyl-benzyl)-benzonitril dihydrochloride (compound 84)**

5 **Compound 82** (45mg, 0.11mol) was dissolved in dry THF (2mL) and cooled to 0°C. Pyridine (36μL, 0.44mg) and trifluoroacetic anhydride (31μL, 0.22mmol) was added and stirring was continued for 1h at 25°C. Water was added and the solution was extracted with ethyl acetate. The organic phase was washed with dilute NaHCO₃ (aq), dried (K₂CO₃) and evaporated *in vacuo*. The residue was treated with HCl in methanol 3h at 50°C. Removal of
10 solvent *in vacuo* and chromatography on silica (CH₂Cl₂/ MeOH/ NH₃, 90:10:1) of residue gave 15mg (49%). Treatment with excess HCl in ether/ methanol gave the dihydrochloride **compound 84** which was precipitated, dissolved in water and freeze-dried. Mp: 141-45°C. IR (KBr) (cm⁻¹): 3400(br), 2700(br), 2230, 1434. MS (free amine): 277, 232, 192, 165. ¹H NMR: (free amine, CDCl₃): δ = 7.58-7.18 (m, 9H, Ar-H), 4.27 (s, 1H, CHAr₂) 2.89, 2.35
15 (2m, 8H, piperazine-H), 1.70 (s, NH). Anal. calc. for C₁₈H₁₉N₃·2HCl · x1H₂O, C:58.70, H: 6.29, N: 11.41. Found C: 58.88, H: 6.46, N: 11.24.

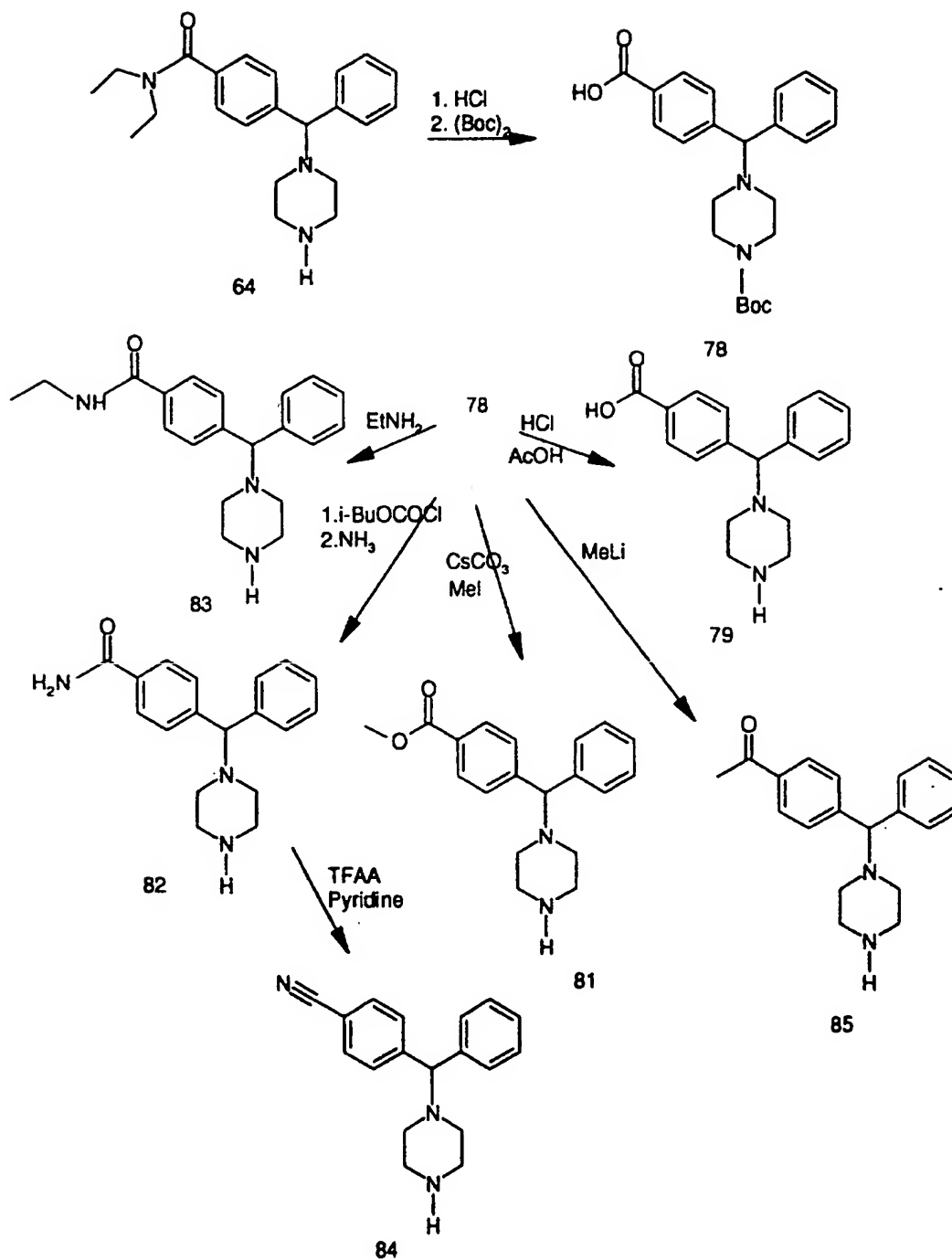
Example 48**Preparation of 4-(1-piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85)**

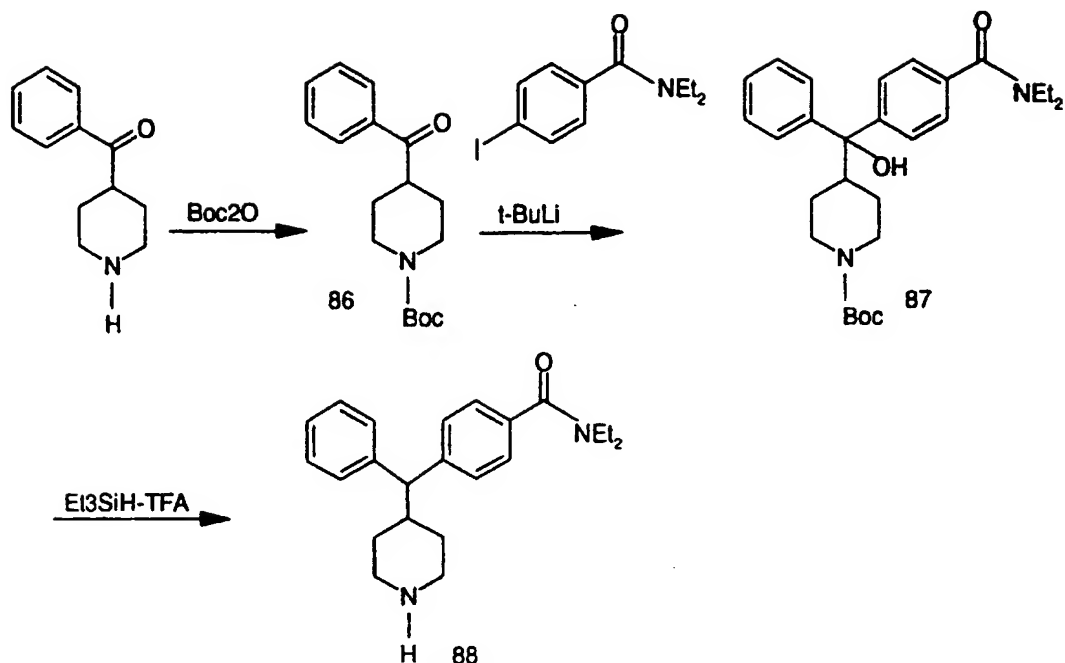
20 **Compound 78** (0.20g, 0.50mmol) was dissolved in dry THF (5mL) and cooled to 0°C under nitrogen. Methyl lithium (3.1mL, 0.8M in ether, 2.5mmol) was added during 1 min and stirring was continued for 2h. Chlorotrimethylsilane (0.63mL, 5.0mmol) was added and
25 the temperature was allowed to reach 25°C, then ammonium chloride (aq) was added. The organic phase was decanted off, evaporated and the residue purified by chromatography on silica (CH₂Cl₂/ MeOH/ NH₃, 95:5:1) to give 0.11g (75%) of ketone without Boc-group. The dihydrochloride salt, **compound 85** was prepared by treatment with excess HCl in ether. Mp: 175-85°C. IR (KBr) (cm⁻¹): 3400(br), 2700(br), 1680, 1607, 1424, 1269. MS
30 (EI, free amine): 294, 249, 209, 165. ¹H NMR: (free amine, CDCl₃): δ = 7.77-7.04 (m, 9H,

Ar-H), 4.22 (s, 1H, CHAr₂), 2.92 (m, 4H, piperazine-H), 2.43 (s, 3H, MeCO), 2.40 (m, 4H, piperazine-H).

Anal. calc. for C₁₉H₂₂N₂O x2HCl x1.6 H₂O, C: 57.61, H: 6.92, N: 7.07. Found C: 57.54, H: 6.75, N: 6.91.

Scheme 14



Scheme 15

5

The compounds according to Example 49 were synthesized as shown in Scheme 15 above.

I.**I. Preparation of 4-benzoyl-N-t-butoxycarbonylpiperidine (compound 86)**

10

A mixture of 4-benzoylpiperidine hydrochloride (6.77 g, 30.0 mmol), di-tert-butylidicarbonate (7.2 g, 33.0 mmol) and KHCO_3 (6.0 g, 60 mmol) in $\text{H}_2\text{O-THF}$ (50/20 mL) was refluxed for 1h. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine, dried over MgSO_4 . Removal of solvents gave 4-benzoyl-N-t-butoxycarbonyl-piperidine (8.54 g, 98 %); δ_{H} (400 MHz, CDCl_3) 1.47 (s, 9H), 1.70 (m, 2H), 1.83 (m, 2H), 2.91 (m, 2H), 3.42 (m, 2H), 4.18 (brs, 2H), 7.46 (m, 2H), 7.56 (m, 1H), 7.93 (m, 2H).

II. Preparation 4-(α -Hydroxy- α -(4-N-t-butoxycarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (compound 87)

5 To a solution of 4-iodo-N,N-diethylbenzamide (3.03 g, 10.0 mmol) and TMEDA (1.28 g, 11.0 mmol) in dry THF (30 mL) was added t-butyllithium (10.0 mL, 1.7 M, 17.0 mmol) at -78°C. After 10 min, 4-benzoyl-N-t-butoxycarbonylpiperidine (2.89 g, 10.0 mmol) in THF (5 mL) was dropwise added. The reaction mixture was warmed to r.t. and then quenched with aqueous NH₄Cl solution and extracted with ethyl acetate (2 x 100 mL). The combined
10 organic layers were washed with brine, dried over MgSO₄. Removal of solvents gave a crude product, which was purified by silica gel column eluting with MeOH-CH₂Cl₂ (0 : 100 → 2 : 98) to provide 4-(α -hydroxy- α -(4-N-t-butoxycarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (MTL 0327, 2.60 g, 56%): m.p.: 100-103°C (CH₂Cl₂): ν_{max} (KBr) cm⁻¹ 3426, 2973, 1687, 1618, 1428, 1289, 1168; δ_{H} (400 MHz, CDCl₃) 1.08 (brs, 3H),
15 1.20 (brs, 3H), 1.30 (m, 4H), 1.41 (s, 9H), 2.50 (t, J=11.2 Hz, 1H), 2.66 (m, 2H), 2.86 (s, OH), 3.22 (brs, 2H), 3.50 (brs, 2H), 4.09 (brs, 2H), 7.18 (m, 1H), 7.26 (m, 4H), 7.45 (m, 4H); $\delta_{\text{C-13}}$ (100 MHz, CDCl₃) 12.8, 14.1, 26.2, 28.3, 39.1, 43.2, 44.3, 53.3, 79.2, 79.4, 125.75, 125.79, 126.2, 126.6, 128.1, 135.1, 145.3, 146.8, 154.6, 171.0.

20 **Example 49**

Preparation 4-((α -4-piperidinyl)-benzyl)-N,N-diethylbenzamide (compound 88)

To a solution of 4-(α -hydroxy- α -(4-N-t-butoxycarbonylpiperidinyl)-benzyl)-N,N-diethylbenzamide (466 mg, 1.0 mmol) and triethylsilane (232 mg, 2.0 mmol) in dry
25 dichloromethane (10 mL) was added trifluoroacetic acid (10.0 mL) at r.t. After 30 min at r.t., more triethylsilane (232 mg, 2.0 mmol) was added. The reaction mixture was stirred for 14 h at r.t., and then condensed. The residue was dissolved in AcOEt (100 mL). The resulting solution was washed with 1 N NaOH solution, aqueous NH₄Cl solution and brine, dried over MgSO₄. Removal of solvents gave a crude product, which was purified by silica
30 gel column eluting with NH₄OH (1 N)-MeOH-CH₂Cl₂ (2.5 : 15 : 82.5) to provide 4-((α -4-

piperidiny]-benzyl)-N,N-diethylbenzamide (245 mg, 70%): m.p.: 160-162°C (CH₂Cl₂);
v_{max} (KBr) cm⁻¹ 3325, 2937, 1613, 1461, 1283, 1095; δ_H (400 MHz, CDCl₃) 1.05 (brs, 3H), 1.07 (m, 2H), 1.19 (brs, 3H), 1.53 (m, 2H), 2.04 (brs, NH), 2.20 (m, 1H), 2.55 (t, J=11.6 Hz, 2H), 3.01 (m, 2H), 3.23 (brs, 2H), 3.51 (d, J=10.4 Hz, 1H), 3.52 (brs, 2H),
5 7.15 (m, 1H), 7.27 (m, 8H); δ_{C-13} (100 MHz, CDCl₃) 12.8, 14.1, 32.2, 39.0, 39.9, 43.1, 46.5, 59.0, 126.1, 126.5, 127.9, 128.0, 128.3, 134.8, 143.0, 144.7, 171.0.

Example 50

10 Preparation of N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide

Procedure as for N,N-Diethyl-4-[(2,5,5-trimethyl-1-piperazinyl)-3-methoxybenzyl]-benzamide. N,N-Diethyl-4-(chloro-3-methoxybenzyl)-benzamide (1.6g, 4.8mmol) was reacted with piperazine (1.6g, 19mmol) in acetonitrile (20mL) for 4 h at 80 °C to give a
15 total of 1.1g product (63%) which was converted into the dihydrochloride salt. Mp: 165-82 °C. IR (amine, CDCl₃ in KBr cell) (cm⁻¹): 3688, 1611, 1458, 1436, 1285. MS(free amine): 381, 336, 296, 224, 196, 165, 152, 112. ¹H NMR: (amine, CDCl₃): δ = 1.05, 1.15 (2 br. s, 6H, 2Me), 2.51, 3.02 (2br. s, 8H, piperazine-H), 3.2, 3.45 (2 br. s, 4H, MeCH₂) 3.72, 3.73 (2s, 3H, MeO), 4.21 (s, 1H, CHAr₂), 4.5 (br. s, 1H, NH), 6.60- 7.40 (m, 8H, Ar-H).
20 C₂₃H₃₁N₃O₂ x2HCl x0.80 H₂O requires: C: 58.92, H: 7.44, N: 8.96. Found: C: 58.98, H: 7.76, N: 8.86.

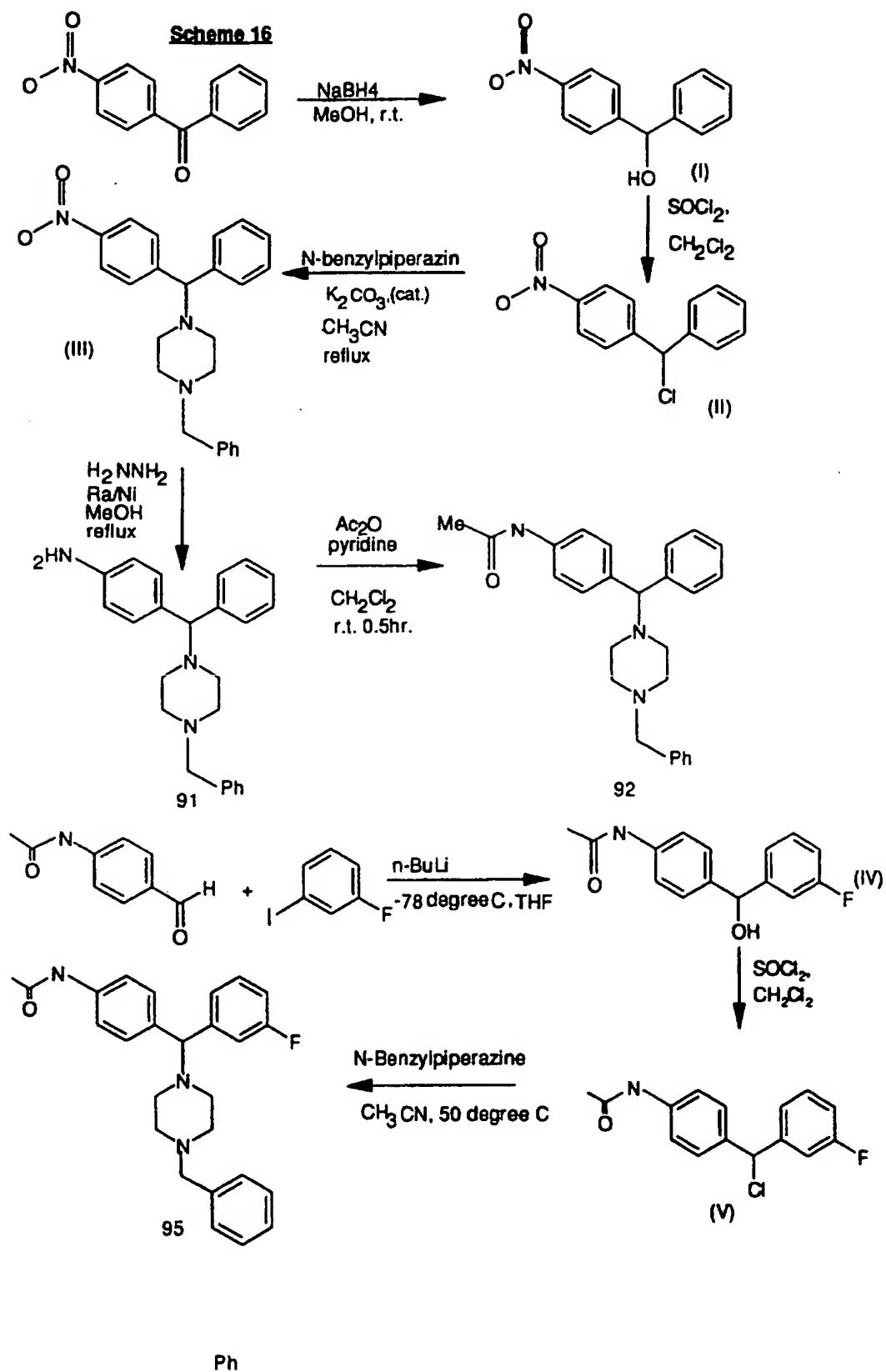
Example 51

25 Preparation of N,N-Diethyl-4-[(4-allyl-1-piperazinyl)-3-methoxybenzyl]-benzamide

Procedure as for N,N-Diethyl-4-[(4-allyl-2,5,5-trimethyl-1-piperazinyl)-3-methoxybenzyl]-benzamide.

N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide (0.16g, 0.42mmol) gave 30mg
30 product (20%) which was converted to dihydrochloride salt. Mp: 151-76 °C. IR (amine,

CDCl₃ in KBr cell) (cm⁻¹): 3688, 1611, 1457, 1435, 1288. MS(free amine): 421, 125. ¹H
NMR: (amine, CDCl₃): δ=1.1 (2 br. s, 6H, 2Me), 2.3- 2.6 (br. s, 8H, piperazine-H), 3.00
(m, 2H, allyl-H), 3.2- 3.5 (2 br. s, 4H, MeCH₂), 3.78 (s, 3H, MeO), 4.20 (s, 1H, CHAr₂),
5.14 (m, 2H, allyl-H), 5.85 (m, 1H, allyl-H), 6.70-7.46 (m, 8H, Ar-H). C₂₆H₃₅N₃O₂ x2HCl
5 x1.4 H₂O requires: C: 60.09, H: 7.72, N: 8.08. Found C: 60.12, H: 7.59, N: 7.88.



The compounds of Examples 52 - 55 were synthesized as shown in Scheme 16 above.

5 **II**

Compound I: 4-(α -hydroxybenzyl)-nitrobenzene

4-nitrobenzoin (4.55g, 20.1mmol) was dissolved in 70ml of anhydrous methanol cooled down to 0°C in an ice bath, NaBH₄ (0.915g, 24.2mmol) was then added under N₂, the mixture was stirred at r.t., for overnight, quenched with NH₄Cl sat'd aqueous solution, MeOH was evaporated and EtOAc was added, the mixture was washed with water, the organic layer was dried over MgSO₄ and concentrated to give a solid as the desired product (~4.58g, ~100% yield).

¹H NMR (CDCl₃, TMS): δ (ppm): 2.40 (s, br, 1H, OH); 5.92 (d, J = 3.2Hz, 1H, Ar-CH-OH); 7.30-7.40 (m, 5H, Ar); 7.58 (d, J =8.6, 2H, Ar-NO₂); 8.18 (d, J =8.6Hz, 2H, Ar-NO₂).

Compound II: 4-(α -chlorobenzyl)-nitrobenzene

Compound I (4.58g, 20mmol) was dissolved in anhydrous CH₂Cl₂, thionyl chloride (4.68g; 39.4mmol) was then added to the mixture under N₂, the reaction mixture was refluxed for 5 hr and was cooled down to r.t., the solvent and excess of thionyl chloride were evaporated under vacuum to give a yellowish solid as the desired product (~100% yield).

¹H NMR (CDCl₃, TMS): δ (ppm): 6.16 (s, 1H, -CH-Cl); 7.30-7.40 (m, 5H, Ar); 7.59 (d, J =8.6Hz, 2H, Ar-NO₂); 8.20 (d, J =8.6Hz, 2H, Ar-NO₂).

25

Compound III: 4-[(N-benzyl-1-piperazinyl)-benzyl]-nitrobenzene

To compound II (1.0g, 4.1mmol) and N-benzylpiperazine (1.45g, 8.2mmol) dissolved in anhydrous acetonitrile, catalytic amount of potassium carbonate was added and the reaction mixture was then refluxed overnight. After cooling down to r.t., the mixture was washed with brine, the organic layer was concentrated under vacuum to give an oil, it was then

30

purified by MPLC using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_4\text{OH}=95/5/1$ as the eluent to give the pure desired product (1.2g, 76% yield).

^1H NMR(CDCl_3 , TMS): δ : 2.41-2.48 (8H, br, piperazin ring), 3.51 (2H, s, Ph-CH_2), 4.34 (1H, s, Ar-CH-Ar), 7.20-8.12 (14H, Ar)ppm.

^{13}C NMR(CDCl_3 , TMS): δ : 51.7, 53.1, 62.9, 75.5, 123.8, 127.0, 128.1, 128.5, 128.7, 129.2, 137.9, 140.9, 146.8, 150.6ppm.

Example 52

Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91)

To compound III (900mg, 2.33mmol) dissolved in 10ml of MeOH, Ra-Ni (150mg) was added and the temperature was increased to 35°C , hydrazine (380mg, 11.63mmol) was then added slowly via a syringe while it was stirring, the temperature of the mixture was increased to 70°C , until the evolution of the gas seized, the reaction mixture was cooled down to r.t., filtered over celite and concentrated to give an oil, which was purified by MPLC using $\text{CH}_2\text{Cl}_2/\text{MeOH}=99/1$ — $99/5$ as the eluent to give a yellowish solid as the desired product (660mg, ~80%yield).

Elemental Analysis Calcd.for: $\text{C}_{24}\text{H}_{27}\text{N}_3 \cdot 0.2\text{H}_2\text{O}$: C, 79.64; H, 7.43; N, 11.55. Found: C, 79.83; H, 7.65; N, 11.64.

IR (NaCl Film): $\nu=2807, 1620, 1513, 1451, 1282, 1137\text{cm}^{-1}$.

^1H NMR(CDCl_3 , TMS): δ : 2.3-2.48 (8H, br, piperazine ring), 3.45 (2H, s, br, $-\text{NH}_2$), 3.48 (2H, s, Ph-CH_2), 4.10 (1H, s, Ar-CH-Ar), 6.51 (2H, m, Ar), 7.11-7.37 (12H, m, Ar)ppm.

Example 53

Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-acetanilide (compound 92)

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (50mg, 0.14mmol) and anhydrous pyridine(excess) were dissolved in anhydrous dichloromethane, followed by the

addition of acetic anhydride (4eq.). The reaction mixture was stirred at r.t., for 30 min. and quenched by H₂O, then washed with sat'd NaHCO₃ aqueous solution and brine, the organic layer was dried over anhydrous MgSO₄, filtered and concentrated to give an oil as the product (44mg, 80%yield).

5

¹H NMR: (CDCl₃, TMS) δ: 2.1(3H, s, -CH₃), 2.3-2.48 (8H, br, pipyrazin ring), 3.48 (2H, s, Ph-CH₂), 4.16 (1H, s, Ar-CH-Ar), 7.20-8.12 (14H, Ar)ppm.

Elemental Analysis Calcd.for: C₂₆H₂₉N₃O. 2.1HCl. 0.3H₂O: C, 64.83; H, 6.64; N, 8.40.

10 Found: C, 64.86; H, 6.64; N, 8.73

Example 54

Preparation of 4-[(N-benzyl-1-piperazinyl)-benzyl]-methanesulfonamide

15

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (100mg, 0.28mmol) and pyridine (excess) were dissolved in anhydrous dichloromethane (5 ml) followed by the addition of methanesufonic anhydride(97.55mg, 0.56mmol), the reaction mixture was stirred at rt. for 20 min. followed by TLC, then it was quenched by adding drop of water, 10 ml of EtOAc was added, the mixture was washed with saturated NH₄Cl aqueous solution and brine, the organic layer was dried over MgSO₄, concentrated and purified by MPLC using CH₂Cl₂/MeOH=99/1~95/5 as the solvent to give the pure product as a white solid (~90mg, ~70%yield).

25 Melting point: 195~200°C(dcp.)

¹H NMR: (CDCl₃, TMS) δ: 2.3-2.48 (8H, br, pipyrazin ring), 2.96 (3H, s, CH₃SO₂), 3.51 (2H, s, Ph-CH₂), 4.21 (1H, s, Ar-CH-Ar), 6.25 (1H, br, S-NH-), 7.10-7.41 (14H, m, Ar)ppm.

30

^{13}C NMR:(CDCl_3) δ : 142.4, 140.2, 137.9, 135.3, 129.2, 129.1, 128.5, 128.1, 127.9, 127.0, 121.0, 75.5, 63.0, 53.2, 51.8, 39.3ppm.

Elemental analysis: Calcd.for: $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_2\text{S} \cdot 0.9\text{H}_2\text{O}$: C, 66.46; H, 6.87; N, 9.30. Found: C, 66.53; H, 6.61; N, 9.23.

Example 55

Preparation of Methyl-N-4-[(N-benzyl-1-piperazinyl)-benzyl]-2-methylacetate

10

To 4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91) (100mg, 0.28mmol), Lithium hydride (2.5mg, 0.3mmol) and 1-bromomethylacetate (44.16mg, 0.28mmol) were mixed in anhydrous THF, the reaction mixture were refluxed for 2 hr. and cooled down to rt., then quenched with drops of water, washed with brine twice, dried over anhydrous MgSO_4 and concentrated to an oil, purified by MPLC using $\text{CH}_2\text{Cl}_2/\text{MeOH}=98/2$ as the solvent to give an oil as the product (~23mg, 20%).

15

IR (NaCl Film): HCl salt

$\nu = 3404(\text{br}), 2922(\text{br}), 1745, 1610, 1517, 1439, 1207\text{cm}^{-1}$

20

^1H NMR: (CDCl_3) δ : 2.40 (8H, br, piperazine ring), 3.50 (2H, s, Ph-CH_2), 3.75 (3H, s, $-\text{O-CH}_3$), 3.85 (2H, d, $J=5.2\text{Hz}$, N-CH_2), 4.12 (1H, s, Ar-CH-Ar), 4.18 (1H, t, $J=5.2\text{Hz}$, Ar-NH-CH_2), 6.49 (2H, d, $J=8.4\text{Hz}$, $-\text{N-Ar}$), 7.14~7.38 (12H, m, Ar)ppm.

Anal. Calcd.for: $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_2 \cdot 3\text{HCl}$: C, 60.17; H, 6.36; N, 7.80. Found: C, 59.97; H, 6.61; N, 7.46.

25

Compound IV: 4-(3-fluoro- α -hydroxybenzyl)-acetonitrile

To 1-Fluoro-3-iodo-benzene (7.53g, 33.9mmol) was dissolved in anhydrous THF and was cooled down to -78°C, n-Butyllithium (2.5M in THF, 33.9mmol) was added slowly into the
5 reaction mixture via a syringe, the mixture was stirred for 10 min. followed by the addition of the solution of 4-Acetamidobenzaldehyde (1.84g, 11.3mmol) in 5ml of dry DME, the reaction mixture was then stirred at -78°C for 30 min. before quenched with NH₄Cl aqueous solution. The organic layer was washed with brine and dried over anhydrous MgSO₄, filtered and concentrated to an oil, purified by MPLC using 10% heptane in CH₂Cl₂ and
10 100%CH₂Cl₂ to give the pure product (1.65g, 56% yield).

¹H NMR: (CDCl₃) δ : 2.14 (3H, s, OCCH₃), 2.55 (1H, s, br, OH), 5.76 (1H, d, J =3.2Hz, Ar-CH-Ar), 7.35 (1H, s, CONH), 6.90~7.50 (8H, m, Ar)ppm.

15

Compound V: 4-(3-fluoro- α -chlorobenzyl)-acetonitrile

This was prepared using the same method as described for the preparation of compound (II) but using compound (IV). It was used directly for the next step reaction without
20 purification.

¹H NMR: (CDCl₃) δ : 2.15 (3H, s, OCCH₃), 6.10 (1H, s, Ar-CH-Ar), 7.84 (1H, s, CONH), 6.90~7.6 (8H, m, Ar), 7.84 (1H, s, CONH)ppm.

25

Example 56**Preparation of 4-[(N-benzyl-1-piperazinyl)-3-fluorobenzyl]-acetanilide (compound 95)**

This was prepared using the same method as described for the preparation of compound
30 (III) but using compound (V).

¹H NMR: (CDCl₃) δ: 2.14 (3H, s, OCCH₃), 2.40 (8H, br, piperazine), 3.51 (2H, s, Ph-CH₂), 4.19 (1H, s, Ar-CH-Ar), 6.80–7.40 (13H, m, Ar)ppm.

ANALYSIS:

- 5 *Anal.* Calcd. for: C₂₆H₂₈FN₃O • 2HCl • 1.6CH₂Cl₂ • 2H₂O: C, 56.24; H, 6.02; N, 7.13. Found: C, 56.29; H, 6.10; N, 6.88.

Pharmaceutical compositions

10

The novel compounds according to the present invention may be administered per orally, intramuscularly, subcutaneously, intraperitoneally, intrathoracically, intravenously, intrathecally and intracerebroventricularly.

- 15 The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

- 20 For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

- 25 A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the

necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid
5 glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin,
10 dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

Pharmaceutically acceptable salts are acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium acetate, camsylate, carbonate, chloride, cetate,
15 dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glucaptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate,
20 subacetate, succinate, sulfate, tannate, tartrate, teoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminium, calcium, lithium, magnesium, potassium, sodium, and zinc.

Preferred pharmaceutically acceptable salts are the hydrochlorides and citrates.

25

The term composition is intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

30

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid from compositions include solutions, suspensions, and emulsions. Sterile water or
5 water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active
10 component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

15 Preferably the pharmaceutical compositions is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparations, for example, packeted tablets, capsules, and powders
20 in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Biological evaluation

A) *IN VITRO* MODEL

Cell culture

5

Human 293S cells expressing cloned human μ , δ , and κ receptors and neomycin resistance were grown in suspension at 37°C and 5% CO₂ in shaker flasks containing calcium-free DMEM10% FBS, 5% BCS, 0.1% Pluronic F-68, and 600 µg/ml geneticin.

10 **Membrane preparation**

Cells were pelleted and resuspended in lysis buffer (50 mM Tris, pH 7.0, 2.5 mM EDTA, with PMSF added just prior to use to 0.1 mM from a 0.1 M stock in ethanol), incubated on ice for 15 min, then homogenized with a polytron for 30 sec. The suspension was spun at
15 1000g (max) for 10 min at 4°C. The supernatant was saved on ice and the pellets resuspended and spun as before. The supernatants from both spins were combined and spun at 46,000 g(max) for 30 min. The pellets were resuspended in cold Tris buffer (50 mM Tris/Cl, pH 7.0) and spun again. The final pellets were resuspended in membrane buffer (50 mM Tris, 0.32 M sucrose, pH 7.0). Aliquots (1 ml) in polypropylene tubes were frozen in
20 dry ice/ethanol and stored at -70°C until use. The protein concentrations were determined by a modified Lowry assay with SDS.

Binding assays

25 Membranes were thawed at 37°C, cooled on ice, passed 3 times through a 25-gauge needle, and diluted into binding buffer (50 mM Tris, 3 mM MgCl₂, 1 mg/ml BSA (Sigma A-7888), pH 7.4, which was stored at 4°C after filtration through a 0.22 µm filter, and to which had been freshly added 5 µg/ml aprotinin, 10 µM bestatin, 10 µM diprotin A, no DTT). Aliquots of 100 µl (for µg protein, see Table 1) were added to iced 12x75 mm
30 polypropylene tubes containing 100 µl of the appropriate radioligand (see Table 1) and 100

5 μ l of test peptides at various concentrations. Total (TB) and nonspecific (NS) binding were determined in the absence and presence of 10 μ M naloxone respectively. The tubes were vortexed and incubated at 25°C for 60-75 min, after which time the contents are rapidly vacuum-filtered and washed with about 12 ml/tube iced wash buffer (50 mM Tris, pH 7.0, 3 mM MgCl₂) through GF/B filters (Whatman) presoaked for at least 2h in 0.1% polyethyleneimine. The radioactivity (dpm) retained on the filters was measured with a beta counter after soaking the filters for at least 12h in minivials containing 6-7 ml scintillation fluid. If the assay is set up in 96-place deep well plates, the filtration is over 96-place PEI-soaked unifilters, which were washed with 3 x 1 ml wash buffer, and dried in an oven at 10 55°C for 2h. The filter plates were counted in a TopCount (Packard) after adding 50 μ l MS-20 scintillation fluid/well.

Data analysis

15 The specific binding (SB) was calculated as TB-NS, and the SB in the presence of various test peptides was expressed as percentage of control SB. Values of IC₅₀ and Hill coefficient (n_H) for ligands in displacing specifically bound radioligand were calculated from logit plots or curve fitting programs such as Ligand, GraphPad Prism, SigmaPlot, or ReceptorFit. Values of K_i were calculated from the Cheng-Prusoff equation. Mean \pm S.E.M. values of 20 IC₅₀, K_i and n_H were reported for ligands tested in at least three displacement curves.

Receptor saturation experiments

Radioligand K_d values were determined by performing the binding assays on cell 25 membranes with the appropriate radioligands at concentrations ranging from 0.2 to 5 times the estimated K_d (up to 10 times if amounts of radioligand required are feasible). The specific radioligand binding was expressed as pmole/mg membrane protein. Values of K_d and B_{max} from individual experiments were obtained from nonlinear fits of specifically bound (B) vs. nM free (F) radioligand from individual according to a one-site model.

B) BIOLOGICAL MODEL (IN VIVO MODEL)**FREUND'S COMPLETE ADJUVANT (FCA), AND SCIATIC NERVE CUFF
INDUCED MECHANO-ALLODYNIA IN RAT****Animals**

- 5 Male Sprague-Dawley rats (Charles River, St-Constant, Canada) weighing 175-200g at the time of surgery were used. They were housed in groups of three in rooms thermostatically maintained at 20° C with a 12:12 hr light/dark cycle, and with free access to food and water. After arrival, the animals were allowed to acclimatize for at least 2 days before surgery. The experiments were approved by the appropriate Medical Ethical Committee for animal
10 studies.

EXPERIMENTAL PROCEDURE**FREUND'S COMPLETE ADJUVANT**

- The rats were first anesthetized in a Halothane chamber after which 10µl of FCA was
15 injected s.c. into the dorsal region of the left foot, between the second and third external digits. The animals were then allowed to recover from anesthesia under observation in their home cage.

SCIATIC NERVE CUFF

- 20 The animals were prepared according to the method described by Mosconi and Kruger (1996). Rats were anesthetized with a mixture of Ketamine / Xylazine i.p. (2ml/kg) and placed on their right side and an incision made over, and along the axis of, the lateral aspect of the left femur. The muscles of the upper quadriceps were teased apart to reveal the sciatic nerve on which a plastic cuff (PE-60 tubing, 2mm long) was placed around. The
25 wound was then closed in two layers with 3-0 vicryl and silk sutures.

DETERMINATION OF MECHANO-ALLODYNIA USING VON FREY TESTING

Testing was performed between 08:00 and 16:00h using the method described by Chaplan et al. (1994). Rats were placed in Plexiglas cages on top of a wire mesh bottom which allowed access to the paw, and were left to habituate for 10-15 min. The area tested was the mid-plantar left hind paw, avoiding the less sensitive foot pads. The paw was touched with a series of 8 Von Frey hairs with logarithmically incremental stiffness (0.41, 0.69, 1.20, 2.04, 3.63, 5.50, 8.51, and 15.14 grams; Stoelting, Ill, USA). The von Frey hair was applied from underneath the mesh floor perpendicular to the plantar surface with sufficient force to cause a slight buckling against the paw, and held for approximately 6-8 seconds. A positive response was noted if the paw was sharply withdrawn. Flinching immediately upon removal of the hair was also considered a positive response. Ambulation was considered an ambiguous response, and in such cases the stimulus was repeated.

TESTING PROTOCOL

The animals were tested on postoperative day 1 for the FCA-treated group and on post-operative day 7 for the Sciatic Nerve Cuff group. The 50% withdrawal threshold was determined using the up-down method of Dixon (1980). Testing was started with the 2.04 g hair, in the middle of the series. Stimuli were always presented in a consecutive way, whether ascending or descending. In the absence of a paw withdrawal response to the initially selected hair, a stronger stimulus was presented; in the event of paw withdrawal, the next weaker stimulus was chosen. Optimal threshold calculation by this method requires 6 responses in the immediate vicinity of the 50% threshold, and counting of these 6 responses began when the first change in response occurred, e.g. the threshold was first crossed. In cases where thresholds fell outside the range of stimuli, values of 15.14 (normal sensitivity) or 0.41 (maximally allodynic) were respectively assigned. The resulting pattern of positive and negative responses was tabulated using the convention, X = no withdrawal; O = withdrawal, and the 50% withdrawal threshold was interpolated using the formula:

$$50\% \text{ g threshold} = 10^{(X+15)} / 10,000$$

where X_f = value of the last von Frey hair used (log units); k = tabular value (from Chaplan et al. (1994)) for the pattern of positive / negative responses; and δ = mean difference between stimuli (log units). Here $\delta = 0.224$.

5

Von Frey thresholds were converted to percent of maximum possible effect (% MPE), according to Chaplan et al. 1994. The following equation was used to compute % MPE:

$$\% \text{ MPE} = \frac{\text{Drug treated threshold (g)} - \text{allodynia threshold (g)}}{\text{Control threshold (g)} - \text{allodynia threshold (g)}} \times 100$$

10

ADMINISTRATION OF TEST SUBSTANCE

Rats were injected (subcutaneously, intraperitoneally, or orally) with a test substance prior to von Frey testing, the time between administration of test compound and the von Frey test varied depending upon the nature of the test compound.

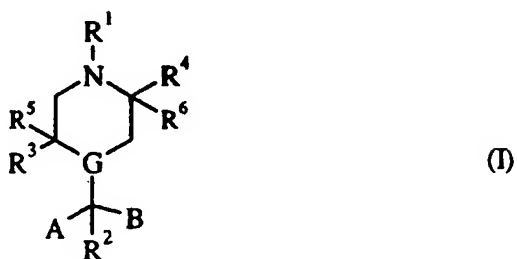
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Claims

1. A compound of the general formula (I)



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wherein

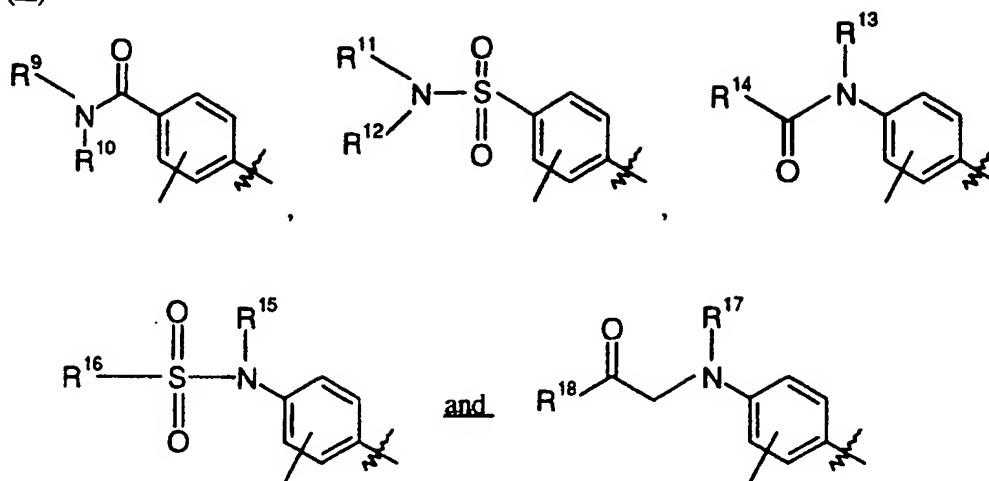
G is a carbon atom or a nitrogen atom;

10 A is selected from

(i) phenyl substituted by any of -COOH, -CONH₂, COOCH₃, -CN, NH₂ or -COCH₃;

15 (ii) naphthyl, benzofuranyl, and quinolinyl; and

(iii)



wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH₃, (CH₂)₀CF₃, halogen, CONR⁷R⁸, CO₂R⁷, COR⁷, (CH₂)₀NR⁷R⁸, (CH₂)₀CH₃(CH₂)₀SOR⁷, (CH₂)₀SO₂R⁷ and (CH₂)₀SO₂NR⁷R⁸ wherein o is 0, 1, or 2, and R⁷ and R⁸ are as defined below;

R¹ is selected from hydrogen; a branched or straight C₁-C₆ alkyl, C₁-C₆ alkenyl, -CO(C₁-C₆ alkyl); (C₁-C₆ alkyl)-B wherein B is as defined below; C₃-C₈ cycloalkyl, C₄-C₈ (alkyl-cycloalkyl) wherein alkyl is C₁-C₂ alkyl and cycloalkyl is C₃-C₆ cycloalkyl; C₆-C₁₀ aryl; and heteroaryl having from 5 - 10 atoms selected from any of C, S, N and O; and whereby the C₆-C₁₀ aryl and the heteroaryl may optionally be substituted by 1 or 2 substituents selected from hydrogen, CH₃, (CH₂)₀CF₃, halogen, CONR⁷R⁸, CO₂R⁷, COR⁷, (CH₂)₀NR⁷R⁸, (CH₂)₀CH₃(CH₂)₀SOR⁷, (CH₂)₀SO₂R⁷ and (CH₂)₀SO₂NR⁷R⁸; wherein o is 0, 1, or 2, and R⁷ and R⁸ are as defined below;

R⁷ and R⁸ is each and independently as defined for R¹ above;

R² is selected from hydrogen, CH₃, OR¹, CO₂R¹, and CH₂CO₂R¹ wherein R¹ is as defined above;

$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}$, and R^{18} , is each and independently as defined for R1 above;

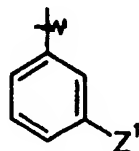
- 5 B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety, each having from 5 to 10 atoms selected from any of C, S, N and O, and each being optionally substituted by 1 or 2 substituents independently selected from hydrogen, CH_3 , CF_3 , halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7 , $(CH_2)_pSOR^7$,
 10 $(CH_2)_pSO_2R^7$, and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, 2 or 3 and wherein R^7 and R^8 are as defined above;

- R^3, R^4, R^5 and R^6 is each and independently selected from
 15 R^7 , $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p(p-OH Ph)$, $(CH_2)_p-3-indolyl$, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$;
 wherein p is 0, 1, 2, 3, or 4, and R^7 and R^8 are as defined above;

- as well as pharmaceutically acceptable salts of the compounds of the formula (I), isomers,
 20 hydrates, isoforms and prodrugs thereof;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a - NH_2 group, B may not be



25

wherein

Z^1 is hydroxy, and esters thereof;
 hydroxymethyl, and esters thereof; or
 amino, and carboxamides and sulfonamides..

5

2. A compound of the formula I according to claim 1, wherein

G is a carbon atom or a nitrogen atom;

A is selected from

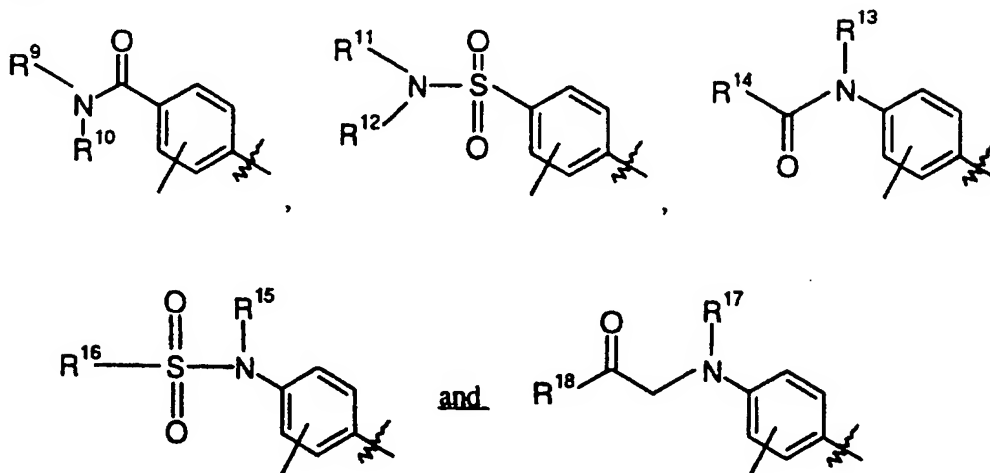
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(i) phenyl substituted by any of $-\text{COOH}$, $-\text{CONH}_2$, COOCH_3 , $-\text{CN}$, NH_2 or $-\text{COCH}_3$;

(ii) naphthyl, benzofuranyl, and quinoliny; and

15

(iii)



20

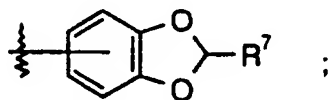
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH₃, (CH₂)_oCF₃, halogen, CONR⁷R⁸, CO₂R⁷, COR⁷, (CH₂)_oNR⁷R⁸, (CH₂)_oCH₃(CH₂)_oSOR⁷, (CH₂)_oSO₂R⁷ and
 5 (CH₂)_oSO₂NR⁷R⁸, wherein o is 0, 1, or 2, and R⁷ and R⁸ are as defined below;

R¹, R⁷ and R⁸ is each and independently selected from hydrogen; a branched or straight C₁-C₄ alkyl, allyl, -CO-(C₁-C₆ alkyl); (C₁-C₆ alkyl)-B wherein B is as defined below; C₃-C₅ cycloalkyl, C₄-C₈ (alkyl-cycloalkyl) wherein alkyl is C₁-C₂ alkyl and cycloalkyl is
 10 C₃-C₆ cycloalkyl; and phenyl;

R² is hydrogen, methyl, or OR¹ wherein R¹ is as defined above;

R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, and R¹⁸ is each and independently as defined
 15 for R¹ above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, pyrrol, furanyl, quinoliny, isoquinoliny, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl,
 20 tetrahydroisoquinoliny, tetrahydrofuranly, pyrrolidinyl, indazoliny, and

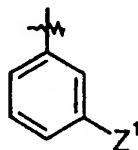


each B group being optionally substituted by 1-2 substituents independently selected from
 25 hydrogen, CH₃, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷, (CH₂)_pCO₂R⁷, and OR⁷,
 wherein p is 0 or 1, and wherein R⁷ and R⁸ are as defined above; and

R^3 , R^4 , R^5 and R^6 is each and independently selected from hydrogen, CH_3 , $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p(p-OH Ph)$, $(CH_2)_p$ -3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$, wherein p is 0, 1, 2, or 3, and wherein R^7 and R^8 are as defined above;

5

with the proviso that when A is a phenyl ring substituted by a $-CN$ group or by a $-NH_2$ group, B may not be



10 wherein

Z^1 is hydroxy, and esters thereof;

hydroxymethyl, and esters thereof; or

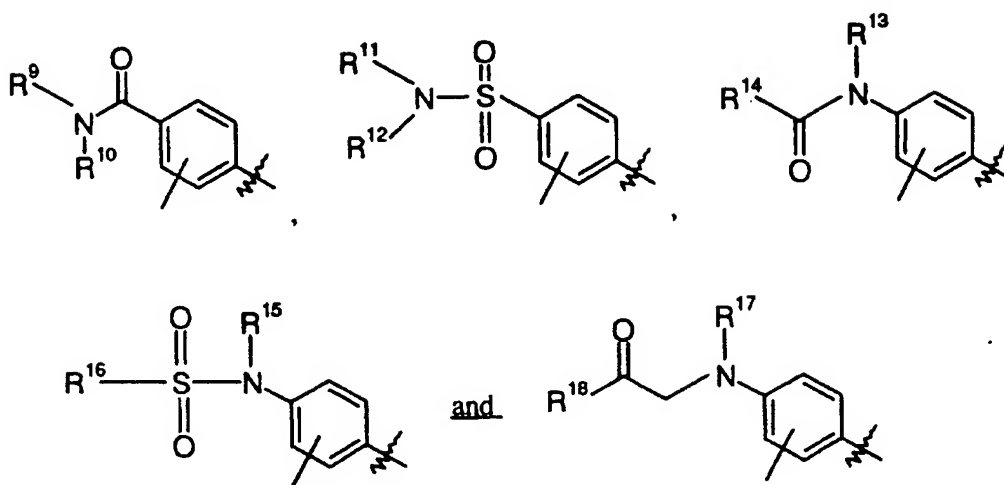
amino, and carboxamides and sulfonamides.

3. A compound of the formula I according to claim 1, wherein

G is a nitrogen atom;

A is selected from

5



10

wherein

$R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}$, and R^{18} is each an ethyl group;

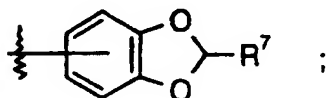
15

R^1 is selected from hydrogen, methyl, ethyl, allyl, or CH_2 -cyclopropyl;

R^2 is H, methyl, or OR^1 ;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinoliny, isoquinoliny, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinoliny, tetrahydrofuranyl, indazoliny, and

5



each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF₃, halogen, (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCOR⁷,
 10 (CH₂)_pCO₂R⁷, and OR⁷,

wherein p is 0, 1, or 2, and wherein R⁷ and R⁸ are as defined for R¹ above;

R³, R⁴, R⁵ and R⁶ is each and independently selected from H, CH₃, CH(Me)₂,
 15 CH₂CH(Me)₂, CH(Me)CH₂CH₃ (CH₂)_pCONR⁷R⁸, (CH₂)_pNR⁷R⁸, (CH₂)_pCONR⁷R⁸,
 (CH₂)_pCO₂R⁷, (CH₂)_pPh, (CH₂)_p(p-OH Ph), (CH₂)_p-3-indolyl, (CH₂)_pSR⁷, and
 (CH₂)_pOR⁷

wherein p is 0, 1 or 2, and wherein R⁷ and R⁸ are as defined above.

20

4. A compound of the formula (I) of claim 1 above, being any one of

(±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 3);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole

5 (compound 4 and 5);

(±)-trans-1-(3-methoxy-α-(2-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 8);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole

(compound 9 and 10);

(±)-trans-1-(3-methoxy-α-(2'-benzofuranyl)benzyl)-2,5-dimethylpiperazine (compound 13);

10 (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole

(compound 14 and 15);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-2-

benzofuranyl)anisole (compound 16 and 17);

(±)-trans-1-(3-methoxy-α-(6'-quinoliny)benzyl)-2,5-dimethylpiperazine (compound 20 and

15 21);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinoliny)anisole

(compound 22);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinoliny)anisole

(compound 23);

20 (±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-6-

quinoliny)anisole (compound 24 and 25);

(±)-trans-1-(3-methoxy-α-(4-quinoliny)benzyl)-2,5-dimethylpiperazine (compound 28);

(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-quinoliny)anisole

(compound 29 and 30);

25 (±) 4-((α-(1-Piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide (compound 33);

(±) 4-((α-((4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide • 2HCl

(compound 34);

(±) 4-((α-(1-Piperazinyl))-2-naphthylmethyl)-N,N-diethylbenzamide (compound 37);

(±) 4-((α-((4-Allyl)-1-piperazinyl))-2-naphthylmethyl)-N,N-diethylbenzamide (compound

30 38);

- (±) 4-((α-(1-Piperaziny))l)-4-xylyl)-N,N-diethylbenzamide (compound 41);
- (±) 4-((α-((4-Allyl)-1-piperaziny))l)-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 42);
- (±) 4-((α-(1-Piperaziny))l)-3-xylyl)-N,N-diethylbenzamide • 2HCl (compound 45);
- (±) 4-((α-(1-Piperaziny))l)-cyclohexylmethyl)-N,N-diethylbenzamide (compound 48);
- 5 (±) 4-((α-(1-Piperaziny))l)-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 51);
- (±) 4-((α-(1-Piperaziny))l)-1-naphtylmethyl)-N,N-diethylbenzamide (compound 54);
- 4-(4-(2-Dimethyl-5-methyl-piperaziny))l)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 57);
- 4-(4-(1-Allyl-2-dimethyl-5-methyl-piperaziny))l)-3-methoxybenzyl)-N,N-diethylbenzamide
- 10 dihydrochloride (compound 58);
- 4-(1-(4-Allyl-2-dimethyl-5-methyl-piperaziny))l)-3-methoxybenzyl)- N,N-diethylbenzamide dihydrochloride (compound 60);
- 4-(1-(2-dimethyl-5-methyl-piperaziny))l)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 61);
- 15 4-((1-piperaziny))l)-benzyl)- N,N-diethylbenzamide dihydrochloride (compound 64);
- 4-((4-Allyl-1-piperaziny))l)-benzyl)-N,N-diethylbenzamide dihydrochloride (compound 65);
- 4-((4-Acetyl-1-piperaziny))l)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77);
- 4-(4-(2-Hydroxymethyl-5-methyl)piperaziny))l)-benzyl)-N,N-diethyl-benzamide dihydrochloride (compound 69);
- 20 4-((4-(2-Hydroxymethyl-5-methyl)piperaziny))l)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 70);
- 4-((4-(1-Allyl-2-hydroxymethyl-5-methyl)piperaziny))l)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 71);
- Methyl 3-((2-naphtyl)-(3-methyl-piperaziny))methyl)phenyl ether dihydrochloride
- 25 (compound 75);
- Methyl 3-((2-naphtyl)-(4-allyl-2-methyl-piperaziny))methyl)phenyl ether dihydrochloride (compound 76);
- 4-((1-piperaziny))l)-benzyl)-benzoic acid dihydrochloride (compound 79);
- 4-((1-piperaziny))l)-benzyl)-N-ethylbenzamide hydrochloride (compound 83);
- 30 Methyl 4-((4-*t*-butoxycarbonyl-1-piperaziny))l)-benzyl)benzoate (compound 80);

- Methyl 4-((1-piperazinyl)-benzyl)benzoate dihydrochloride (compound 81);
4-(1-piperazinyl-benzyl)-benzonitril dihydrochloride (compound 84);
4-(1-piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85);
4-((α -4-piperidinyl)-benzyl)-N,N-diethylbenzamide (compound 88);
5 N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide (Example 50);
N,N-Diethyl-4-[(4-allyl-1-piperazinyl)-3-methoxybenzyl]-benzamide (Example 51);
4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91);
4-[(N-benzyl-1-piperazinyl)-benzyl]-acetanilide (compound 92);
4-[(N-benzyl-1-piperazinyl)-benzyl]-methanesulfonamide (Example 54);
10 Methyl-N-4-[(N-benzyl-1-piperazinyl)-benzyl]-2-methylacetate (Example 55); and
4-[(N-benzyl-1-piperazinyl)-3-fluorobenzyl]-acetanilide (compound 95).

5. A compound according to any of claims 1-4, in form of its hydrochloride salt.
- 15 6. A compound according to any of claims 1-5, for use in therapy.
7. A compound according to claim 6, wherein the therapy is pain management.
- 20 8. A compound according to claim 6; wherein the therapy is directed towards gastrointestinal disorders.
9. A compound according to claim 6, wherein the therapy is directed towards spinal injuries.
- 25 10. A compound according to claim 6, wherein the therapy is directed to disorders of the sympathetic nervous system.
11. Use of a compound according to any of claims 1-5 for the manufacture of a
30 medicament for use in the treatment of pain.

12. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

5 13. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of spinal injuries.

14. A compound according to any of claims 1-5, further characterized in that it is isotopically labelled.

10

15. Use of a compound according to claim 14 as a diagnostic agent.

16. A pharmaceutical composition comprising a compound according to any of claims 1-5 as an active ingredient, together with a pharmaceutically acceptable carrier.

15

17. A process for the preparation of a compound according to any of claims 1-5, whereby

20 A) (i) An aldehyde or ketone is treated with a nucleophile, giving the corresponding alcohol;
(ii) the alcohol is converted into a suitable leaving group, which in turn is displaced with a nucleophile; and
(iii) a N-(4)-unsubstituted piperazine derivative is substituted via its organo halide or
25 equivalent species, or acylated; or

B) (i) A N-protected amino acid ester is reacted with a second amino acid ester, and thereafter treated with an acid, giving a piperazinedione;
(ii) the dione is reduced to the corresponding piperazine; and
30 (iii) the piperazine is alkylated or acylated on one or more of the nitrogens.

18. A method for the treatment of pain, whereby an effective amount of a compound according to any of claims 1-5 is administered to a subject in need of pain management.

1
INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/01635

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 241/04, C07D 295/04, A61K 31/495, A61K 51/04
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 April 1997

Date of mailing of the international search report

09 -04- 1997

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01635

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01635

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01635

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INTERNATIONAL SEARCH REPORT
Information on patent family members

04/03/97

International application No.
PCT/SE 96/01635

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